Draft Guidance for Industry and FDA Staff

Investigational Device Exemption (IDE) Guidance for Retinal Prostheses

DRAFT GUIDANCE

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For questions regarding this document, either contact Ethan Cohen, Ph.D. at 301-796-2485, ethan.cohen@fda.hhs.gov or Everette Beers, Ph.D. at 240-276-4200, everette.beers@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Vitreoretinal and Extraocular Devices Branch
Division of Ophthalmic and Ear Nose and Throat Devices
Office of Device Evaluation

Preface

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Draft Guidance for Industry and FDA Staff

Investigational Device Exemption (IDE) Guidance for Retinal Prostheses

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance is intended for FDA staff reviewers and members of industry who intend to file an investigational device exemption (IDE) with the FDA to conduct feasibility and/or pivotal human clinical trials of their retinal prostheses in the United States to support a pre-market approval application (PMA).

This document provides guidance about developing pre-clinical and clinical tests of retinal prosthetic devices. This guidance describes pre-clinical tests that you should conduct to characterize device safety before initiating any clinical testing.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to retinal prosthetic devices and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or

recommended, but not required. The use of the word *must* means that something is required. For the purposes of this guidance, "you" refers to the sponsor of the IDE investigation and "we" refers to FDA.

This device specific guidance document is in addition to other FDA publications on PMA or IDE applications and is not a replacement for those documents. The CDRH Device Advice website has additional information about PMA (21 CFR 814)[1] and IDE (21 CFR Part 812)[2] submissions.

We recommend that you use this document as you develop data to support an IDE application. The non-clinical and clinical tests mentioned in the guidance represent FDA's current thinking based on the information available at this time. Additional information that becomes available at a later date may suggest alternative test methods or functional assessments that may be more appropriate to assess the safety and effectiveness of retinal prostheses. The Division of Ophthalmic Ear, Nose and Throat Devices (DOED) is available to discuss clinical trial designs, test protocols, and proposed indications for use.

This guidance cites a number of voluntary standards which are recognized by FDA. You may access a list of the FDA-recognized standards from the CDRH web site[3] or the guidance, **Recognition and Use of Consensus Standards**.[4] See Appendix A for a list of the voluntary standards referenced in this guidance.

2. Scope

This document is limited to retinal prostheses, i.e., visual prosthetic devices implanted on or beneath the retina, or on the outer surface of the globe, that use electrical stimulation to provide some level of visual stimulation for persons suffering from degenerative retinal conditions.

This document does not apply to prostheses that stimulate the optic nerve or other higher brain areas such as the visual cortex or the lateral geniculate nucleus. In addition, prostheses that incorporate drugs or biological products may be combination products. The FDA Center with regulatory responsibility for a combination product is determined by the product's primary mode of action. For additional information on combination product jurisdiction, please refer to the FDA Office of Combination Products.[5]

FDA believes that the devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m).[6] Sponsors intending to use these devices in a clinical investigation must therefore submit an IDE application to FDA and obtain FDA approval of the

[1] http://www.fda.gov/cdrh/devadvice/pma/
[2] http://www.fda.gov/cdrh/devadvice/ide/index.shtml
[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
[4] http://www.fda.gov/cdrh/osel/guidance/321.html
[5] http://www.fda.gov/oc/combination
[6] http://www.fda.gov/oc/ohrt/irbs/devices.html#risk

application before beginning the investigation (21 CFR 812.20(a)). In addition to the requirement of obtaining an FDA-approved IDE (21 CFR Part 812), sponsors of such studies must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).[7]

3. Device Description

Your IDE application must include the complete investigational plan or, where appropriate, a summary of the investigational plan. 21 CFR 812.20(b)(2). In your investigational plan you must include a description of the prosthetic device and its functional components (21 CFR 812.25(d)). Your description should include:

- pictorial representations,
- engineering drawings,
- block diagrams of circuits, and
- block diagrams of software interfaces.

The block diagrams of the circuits should trace signal flow, processing, and logic of operation at the system level and the circuit level as appropriate.

Your description of each functional component should include:

- a complete set of electrical schematics,
- a complete set of mechanical drawings,
- detailed drawings and descriptions of all components including material composition and coatings,
- electrical specifications and, where appropriate, references to laboratory testing that established these specifications,
- mechanical specifications and, where appropriate, references to laboratory testing that established these specifications,
- an explanation of how the implant design accommodates human eye and head size variation,

[7] You should review the statutory definition of "applicable clinical trial" to determine if your trial must be registered to comply with the law. *See* Pub. L. No. 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)), available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf. Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page at http://prsinfo.clinicaltrials.gov.

- detailed engineering drawings of the electrode(s) in the stimulation array, their number, dimensions, spacing, material composition, insulation, flexibility, and the surface area/thickness of any coatings, and
- detailed descriptions of any cabling including: their interconnects from the electrodes to the application specific integrated circuit (ASIC), their conductors, and their insulation layers or associated coatings.

A. Video Camera/Transducer and Attachments

If your device utilizes a component to capture a picture of an image, we recommend you describe the following:

- the type of photosensor or video input and processor used with the retinal implant,
- the resolution and configuration of its sensors, sensor location, low-light sensitivity, field of view, and ability to encode contrast in the visual scene,
- any eye tracking capabilities, and
- the means of attachment of any external connectors, transmitters, telemetry coils, visual processors, and spectacles.

We also recommend you describe the effects of coil distance and eye movements on telemetry data transmission during use.

B. Device Accessories

We recommend that you describe all device accessories used for programming, clinical fitting, testing, or home use of your device. You should include pictorial representation, engineering drawings, block diagram circuits, and block diagrams of software interfaces for accessories such as user controls, eye trackers, programming interfaces, software, cameras, spectacles, video processors, cables, connectors, and projection equipment. In addition, we recommend you describe the type of battery used in the device and the recharging unit.

4. Risk Analysis

You must include in your investigational plan a description and analysis of all increased risks to which subjects will be exposed by the investigation, as well as the manner in which these risks will be minimized (21 CFR 812.25(c)). You should describe in the IDE application the method you used to conduct this risk analysis and, in so doing, include sufficient detail to support the chosen method.

To fulfill this risk analysis requirement, we recommend that you perform a Failure Mode and Risk Analysis summary on the electronic components and circuitry. Your Failure Mode and Risk Analysis summary should identify and assess the risks due to any potential electronic hazards/failures, the potential severity of these risks, and how to eliminate or reduce them. We

recommend you supply a traceability matrix showing how you validated your risk mitigation features in the electronics of your visual prosthetic device.

5. Content and Format of Test Data

In your IDE application you must include a complete report of prior investigations of the device (21 CFR 812.20(b)(2)). This report must include information on all prior clinical, animal, and laboratory testing of the device, whether adverse or supportive, a bibliography of all relevant publications, whether adverse or supportive, and a summary of all other relevant unpublished information, whether adverse or supportive, that is in your possession or reasonably obtainable by you (21 CFR 812.27(a)-(b)). This report must be comprehensive and adequate to justify the proposed investigation (21 CFR 812.27(a)).

We recommend that you present the test data in your IDE application in a summary format that includes the elements described below.

A. Table of Contents

We recommend you include a table of contents near the front of the document that lists the specific tests that were performed.

B. Tests Performed, Data Summaries, and Conclusions

For each test performed, you should state the study objective, method (protocol) used, results, and conclusions. As applicable to your device, the report should contain:

- minimum measured value (min),
- maximum measured value (max),
- mean, and
- standard deviation of the test data (std. dev.).

We also recommend that you provide a narrative summary of your conclusions for each test conducted and explain whether the results support the safety and performance of your device.

6. Pre-clinical Tests

If you provide information on nonclinical laboratory studies in your application, you must state whether such studies complied with 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR 812.27(b)(3)). If such studies were not conducted in compliance with these regulations, you must state the reason(s) for noncompliance (21 CFR 812.27(b)(3)).

We recommend including the following testing information in your application. If you choose not to include any of the following information, you should explain why you believe such information is not relevant to your device.

A. Materials and Biocompatibility

You should completely describe the material compositions used in your retinal prosthetic device. For all implant material or material contacting the subject, provide detailed specifications for the formulation or chemical composition of any new materials, particularly materials with no history of intraocular or implant use. We recommend you describe the formulations of all device materials by their generic name.

You should provide material biocompatibility profiles for all subject-contacting device components, as described in the FDA guidance **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing**.[8] We recommend that you document the biocompatibility of the device and its associated insertion tools by conducting appropriate tests with the finished device or a facsimile that has undergone similar manufacturing processing, including sterilization. Literature and/or test references for the same material which has undergone the same manufacturing process are generally acceptable. You should also include histology evaluation, where applicable.

Bacterial Endotoxin Testing (Pyrogenicity)

We recommend you provide bacterial endotoxin test results on implanted device components using a validated test method that includes inhibition and enhancement testing. The endotoxin level should be tested as described in the FDA guidance document, **Guideline on Validation of the Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices**[9] or USP 30:2007, <85> Biological Tests and Assays, Bacterial Endotoxin Test (LAL).

B. Animal Tests

We recommend that you conduct animal testing on an active finished device (one that can be turned off) to establish adequate safety before commencing a substantive human trial. We recommend that you design a staged testing approach that includes evaluation of several animals which are implanted long term.

Since implantation may induce failure modes not predicted by device bench testing, we recommend that animal studies evaluate the ocular tissue biocompatibility of the implanted prosthetic device and its associated components and stimulation arrays. The unimplanted

[8] http://www.fda.gov/cdrh/g951.html
[9] http://www.fda.gov/ohrms/dockets/dockets/05d0047/05d-0047-bkg0001-Tab-10.pdf

eye may be used for comparison. The animal studies test reports should include the following items:

- study protocol and objective,
- study design including the species, strain and number of animals used,
- stimulation levels and rates used (if present),
- visually-evoked response testing (if present) such as electroretinograms or visually- or electrically- evoked potentials, and
- histology of the eye and retina with particular attention to regions of device implantation or attachment.

We also recommend you provide an analysis of the animal testing data and a description of any modifications made to the device as a result of this testing.

Acute Tests

You should test the prosthesis electrodes to stimulate the retina near their maximal limits in an animal model for a period of two days. The animal may be sedated. After testing, you should perform a histological examination of the eye and its layers.

Long Term Tests

You should implant the final form of the fully functional retinal prosthetic device in the eye of a model animal for at least six months. The device does not have to be activated and stimulating for the entire duration of implantation to verify device functionality. It may be appropriate to test the device (have it active and stimulating) only within the first two weeks after implantation and again just before explantation to characterize the device's functionality.

After explantation, you should examine the eye and its layers histologically for any pathology associated with the implant. We also recommend you evaluate the explanted device for any failure mechanisms such as corrosion or insulation degradation.

C. Electrode Stimulation Tests

You should report the stimulation testing range and limits for the electrodes in the array. For each electrode tested, we recommend you describe the following items:

- the range of stimulation values you plan to test in subjects,
- whether the pulses are current- or voltage-regulated,
- whether the stimulation is bipolar or monopolar,
- the pulse charge densities to be tested in mC/cm^2 per phase,
- the charge/phase delivered,
- the pulse sequence and polarities, for example, monophasic or biphasic,

- the frequencies of pulse/train stimulation you plan to test,
- the waveforms and duration/phase of the pulses/pulse trains you plan to test,
- the resistance of the electrodes,
- the maximal voltage delivered per pulse,
- whether the pulses are capacitatively-coupled, charge-balanced or asymmetric, and
- the leakage resistance of the electrodes to the stimulator case, if applicable.

We recommend you also describe briefly how the maxima of the above stimulation parameters will overlap in subject tests on single electrodes. For example, you should describe the test's maximal pulse charge density, pulse frequency, and stimulus duration.

D. Durability Tests

We recommend you plan for and begin to conduct the durability testing described below. Prior to initiating human studies you should be able to provide an estimate of these parameters.

Design Lifetime and Performance Durability Tests

We recommend that you describe the design lifetimes for both the implanted and external device components. We recommend you address the durability of the stimulation electrodes by conducting a series of accelerated lifetime tests to evaluate the durability of the electrodes/electrode arrays to electrical stimulation toward the prosthetic design lifetime. We recommend you perform these tests at the maximal stimulation rate in a saline bath at 37^{o}C or higher.

You should also assess the durability of the implant by performing a series of accelerated lifetime tests. These tests should evaluate the durability of the complete implant, mounts, bands, and telemetry coils (if present) to maximal rate stimulation, power reception, and telemetry. In addition we recommend you assess the durability of the external device components by performing a series of lifetime tests on the external visual processor electronics, optical sensors, and telemetry coils (if present).

Calculation of Estimated Lifetimes

We recommend that you relate the outcome of your device lifetime tests to the stress, hermeticity, corrosion and fatigue test analysis results performed. You should include documentation about how the estimated device lifetime was derived from the tests conducted. We recommend you describe all failure modes and effects found in your device tests, and the criticality of any failures found.

Hermeticity Tests

A key factor in determining the lifetime durability of the prosthetic device is maintaining device hermeticity. We recommend you supply data on the design to be used in the clinical study using accelerated lifetime tests. You should test the device until failure.

We recommend you evaluate the hermeticity of your complete device using product lifetime immersion tests in a saline solution at 37°C or higher. Tests that evaluate the items listed below may be done concurrently.

Evaluation of Coating Durability

For devices and their associated cable assemblies coated with water-resistant films, we recommend you provide a study demonstrating that your coating remains effective after immersion testing. We recommend you validate the test. We also recommend you report any cracks, delamination, or scratches, and their observed dimensions. You should substantiate the level of magnification that you use in your inspection method, based on the size of the defect that would cause device failure.

Potential for Corrosion

We recommend that you evaluate the potential for corrosion in designs that allow micromotion between components, such as cable interconnects or suture holes that may disrupt an associated insulation coating or passive film.

Welding, Bonding Patency Tests, and Process Validation

We recommend you validate the adequacy and reliability of any welding or bonding processes used in device fabrication, and their inspection methods. We recommend you describe the inspection process of how device hermeticity of the case (if present) and cabling is validated and determined. We recommend you describe any validation tests performed such as helium leak tests or impedance spectroscopy.

Flexion Testing

We recommend you conduct tests of your retinal prosthesis that simulate the actual forces experienced under flexion when it is mounted in its intended location on or in the eye. We recommend you conduct the tests in saline, at 37°C or greater.

- To assess surgical insertion stresses, we recommend you demonstrate how your device and its cables will withstand surgical implantation, suturing, and any folding. We recommend that you explain the clinical relevance of the loading conditions used for the accelerated durability testing.

- You should also assess flex stresses exerted during normal eye movement. We recommend you perform long-term durability testing that models the physiological loads and boundary conditions that your retinal prosthesis and its cables are likely to experience in its intended ocular location, under normal visual function and daily saccadic eye movement.

E. Electronics

We recommend you supply accurate specifications and fabrication data supporting the implant's design, circuitry, ASIC, interconnects, cabling, and transmission coils.

Eye Orientation and Radio Frequency Link Safety
If the unit uses an external power source and signal, you should supply documentation showing how power is received by the implant through the full range of eye rotational angles. We also recommend you include safety data documenting how the device responds to loss of power or signal in response to excessive rotation of the eye.

Eye Movements
If your device contains a camera or optical sensor not mounted directly to the eye itself, you should document how your device will respond to the subject's eye movements.

Safeguards
You should describe the safety features built into the device such as EMI rejection filters, DC current leakage detection, recovery from power loss, electrode stimulation limits, error logs, software watchdogs and resets to validate proper device function.

Batteries
We recommend you describe the type of battery used in the device and indicate the projected battery life. You should indicate whether the battery is disposable or rechargeable, and how the battery is replaced. In addition, you should describe any protection against inserting the battery with incorrect polarity.

Mobile Unit Controls
We recommend you describe how the portable subject controller of your retinal prosthesis addresses usability, if applicable (i.e., human factors):

- audible machine state indicators or warnings,
- tactilely discernable instrument controls,
- impact resistance,
- presence of an accessible safety or power cutoff switch,
- water and perspiration resistance, and
- ease of battery insertion for replacement.

We recommend you review the FDA guidance on human factor design in instrument control, **Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management--Identifying, Understanding, and Addressing Use-Related Hazards (July 18, 2000).**[10]

F. Software

We recommend you describe in detail the physician fitting software, device programming, patient software controls, and protections against excessive stimulation levels. We also

[10] http://www.fda.gov/cdrh/humfac/1497.pdf

recommend you describe how the software is configured for home use and user adjustment. We recommend you address the following issues, as applicable to your device:

- any failsafes,
- resets and presets,
- software validation tests,
- power down/recovery,
- low power situation,
- device feedback of proper function,
- software limits on device outputs, and
- any protection against user or clinician programming error.

In addition, we recommend you validate all patient and clinician software as described in **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices** (the Software guidance).[11] The kind of information we recommend you submit is determined by the "level of concern," which is related to the risks associated with software failure. The level of concern for a device may be minor, moderate, or major. The Software guidance describes how you should assess the level of concern for an individual device. You should also refer to the guidance, **General Principles of Software Validation**.[12]

G. Visible and Electromagnetic Radiation, and MRI compatibility

We recommend you demonstrate reasonable assurance that use of the device results in neither serious bodily injury nor device malfunction or failure due to electromagnetic emission or interference. We suggest you also describe the radiopacity of the unit and its associated implanted components.

Visible or IR Emission

If the device or any of its components emit visible or infrared (IR) radiation into the eye, we recommend you evaluate the radiation levels and compare them to levels noted in ISO 15004-1,2 Ophthalmic instruments -- Fundamental requirements and test methods or ISO 10939:2007 Ophthalmic instruments -- Slit-lamp microscopes or equivalent.

If diffuse illumination of the eye is employed by the device (e.g., IR illumination for pupil tracking), we recommend you document that the irradiance does not exceed ANSI RP27.1 standard: Photobiological Safety for Lamps and Lamp Systems-General Requirements or equivalent.

Electromagnetic Compatibility

[11] http://www.fda.gov/cdrh/ode/guidance/337.html
[12] http://www.fda.gov/cdrh/comp/guidance/938.pdf

We recommend you evaluate your retinal prosthesis for compatibility with electromagnetic interference from various field strength magnetic resonance imaging (MRI) scanners, metal detectors, high voltage sources and devices emitting strong magnetic fields. Other devices that should be evaluated if applicable include common wireless communication devices, diathermy units, and cardiac defibrillators.

For electromagnetic compatibility testing of the external device components, we recommend you follow IEC 60601-1-2 Medical Electrical Equipment - Part 1: General Requirements for Safety; Electromagnetic Compatibility – Requirements and Tests (General) or an equivalent method. See also the information, "**Electromagnetic Compatibility - EMC**" on FDA's website.[13]

MRI Compatibility

We recommend you inform the subject and the dispensing physician of any MRI or EMC exposure hazards and incompatibilities associated with the retinal prosthesis such as metal detectors, radiofrequency identification (RFID), wireless devices, or subways, among others.

H. Sterilization and Packaging

We recommend you describe the sterilization process for each part of the retinal prosthesis, such as the implant component and surgical insertion tools. Portions of the device that are implanted or that contact breached skin or tissue should be sterilized to a sterility assurance level (SAL) of 10^{-6}. Whenever possible, the device should be sterilized in its final package.

We recommend you describe the validation of each sterilization process, with reference to any sterilization standards you have followed. You should describe the packaging for each device or component and include package integrity testing to support the ability of the packaging to maintain sterility.

If the device is sterilized by ethylene oxide, ethylene oxide residual levels for the intraocular portion of the device should be consistent with the levels specified for intraocular lenses in ANSI/AAMI/ISO 10993-7 Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals and its associated report: TIR 19:1998 Guidance for ANSI/AAMI/ISO 10993-7 or equivalent.

We recommend you use the following sterilization and packaging standards for devices sterilized by the applicable method:

- ANSI/AAMI/ISO 11134 Sterilization of health care products - Requirements for validation and routine control of industrial moist heat sterilization,

[13] http://www.fda.gov/cdrh/emc/

- ANSI/AAMI/ISO 11135 Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices
- ANSI/AAMI/ISO 11137 Sterilization of health care products - Radiation - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices, and
- ANSI/AAMI/ISO 11607 Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes, 1ed.

7. Clinical Tests

You must submit a written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound (21 CFR 812.25(b)). We recommend you provide an overview in your IDE application of all anticipated phases of the clinical investigation, outlining the studies you plan to conduct at each phase. Specifically, you should describe in detail the initial feasibility study and provide an overview of your later phase studies (i.e., studies to refine clinical metrics or device design), if they are already in the planning stages.

Since IDE clinical testing generally follows a phased approach, the sections on clinical testing and device labeling will have different levels of importance for feasibility study protocols compared to pivotal studies of later device designs intended to support a PMA application.

Generally, it is not possible to describe the pivotal study of the final device design before completing the initial phases, because the outcome of the initial study phases are unknown and will influence the design of the pivotal study. However, for each planned clinical study we recommend you provide:

- data to support the safety and longevity of the device,
- pre-clinical animal implant studies in support of the proposed clinical studies,
- the indications for use, which should include the target patient and disease populations,
- the study type (e.g., pivotal, expansion, or feasibility trial),
- the design of the study, including objectives, any masking, randomization, and controls or shams used for comparison,
- the total time planned for subject follow-up,
- the number of subjects you plan to enroll,
- the number of investigational sites, both inside and outside the U.S.,
- the participating investigators, if known,
- the subject inclusion and exclusion criteria,

- the primary safety and effectiveness (visual improvement) endpoints described as specific objective clinical targets,
- any secondary endpoints, such as subject assessment of functional low vision performance,
- study plan with tests and time table for pre- and post-operative evaluation of the visual performance of the subjects,
- testing methodologies, and
- the stimulation range, rates, and levels you plan to test in the subjects.

The study conducted under the IDE should include a control. We recommend you describe the control subjects and control test conditions you plan to use. For active devices that can be switched off, we recommend you also conduct clinical testing with the device switched off. For passive devices that cannot be inactivated, we recommend you evaluate whether a sham implant procedure could be incorporated into the pivotal clinical study. Sham controlled studies represent one study design and choice of control group which may allow for discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors such as patient or observer expectations. This type of study design may be most appropriate for studies with subjective endpoints, such as reduction in patient-reported symptoms. Sham surgical procedures/treatments typically involve more risk than the placebo control arm in drug trials and should be used in limited circumstances. This study design should only be considered when it is methodologically necessary, i.e., when designs that are unblinded are methodologically unacceptable (e.g., because endpoints are subjective) and when a "no treatment" control is methodologically required. Furthermore, the withholding of treatment should not lead to serious harm, such as death or irreversible morbidity. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that investigators, institutional review boards, and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully considered and planned.

To avoid compromising demonstrations of clinical safety or effectiveness in your IDE studies, we recommend that subjects be operated on only to implant the test device and not simultaneously to correct other ocular conditions such as cataract. We also recommend you document the reasons for exclusion of any subjects from the sample population.

A. Unanticipated Adverse Device Effects

Investigators must report all unanticipated adverse device effects[14] to the sponsor and all reviewing IRBs, in accordance with 21 CFR 812.150(a)(1). Unanticipated adverse device effects are defined in 21 CFR 812.3(s). They could include, but are not limited to,

[14] Many in industry may use the term "adverse events" instead of "adverse effects." The term "adverse effects" is the term used in the IDE regulations. See 21 CFR 812.3(s), 21 CFR 812.5(a), 21 CFR 812.38(c), 21 CFR 812.46(b), 21 CFR 812.140(a)(3) & (b)(5), and 21 CFR 812.150(a)(1) & (b)(1).

the following: retina and macular pathologies following surgery, migration or extrusion of prosthesis, uveitis, endophthalmitis, and electric shock.

Sponsors must immediately conduct an evaluation of any unanticipated adverse device effects in accordance with 21 CFR 812.46(b). They must report the results of such evaluations to FDA and all reviewing IRBs within 10 working days after first receiving notice of the adverse effect. 21 CFR 812.150(b)(1). In such reports, we recommend that sponsors describe any use of a Clinical Events Committee, a Data and Safety Monitoring Board, or a core laboratory for adverse effect adjudication.

B. Clinical Safety Endpoints

Other than for initial feasibility studies of limited enrollment, which usually involve fewer than 10 subjects, you should identify a primary safety endpoint to capture surgical complications and potential longer-term adverse events. We recommend that you base your primary safety endpoint on cumulative and persistent rates of a group of adverse event rates obtained from the medical literature for similar ocular invasive retinal surgery procedures, such that all events do not exceed a target rate. You should provide justification for your selection of the cumulative adverse events and for your chosen target rate. This will establish the minimum acceptable safety threshold for your investigation. Additionally, the statistical analysis plan for your pivotal trial should indicate that your planned sample size provides a sufficient number of patients to evaluate this endpoint to demonstrate a reasonable assurance of safety.

C. Clinical Effectiveness Endpoints - Visual Performance Tests

Pre-operative Assessment of Subject Abilities and Performance Variability
A critical metric for demonstrating device effectiveness is documenting the subject's visual performance before device implantation. Severely visually impaired subjects tend to exhibit variable performance on daily vision tests, which can confound statistical analysis of the effectiveness of the implant. In the IDE application, as part of the written protocol, we recommend that you:

- describe the tests you may perform to assess the subject's residual visual capabilities,
- describe how you will sample the subject's visual performance three times on three different days preoperatively,
- describe the inclusion and exclusion criteria along with any tests you may perform to assess concomitant disease, including an evaluation of subjects' mental health status,
- define an age range for participants, and
- describe the range of visual acuities and visual conditions considered acceptable for subject enrollment in the study.

Primary Effectiveness Endpoints

Primary clinical endpoints of acuity provide quantitative documentation of implanted subjects' performance in support of device effectiveness. All testing should be done through an undilated pupil. We recommend that you use the test procedures described below, as appropriate to your device.

Low Vision Letter Acuity

We recommend the study protocol evaluate visual acuity using validated letter chart tests for low vision. Manual acuity levels such as "count fingers" do not provide an adequate quantitative measure of visual performance. We recommend your tests place limits on the subjects' response time.

Grating Acuity

We recommend you test subjects for full-field grating acuity using a forced-choice paradigm and fixed time interval of presentation. We recommend you also evaluate subjects using stimuli projected in a darkened room. A staircase testing procedure may be employed to aid in determining the grating resolution threshold. You should include grating spatial frequencies that cover the entire acuity range specified by the study inclusion criteria. In addition, we recommend you evaluate the subject's ability to detect grating contrast.

Secondary Effectiveness Endpoints

Secondary clinical endpoints provide qualitative documentation of the implanted subject's performance in real world situations. Secondary clinical endpoints may also be appropriate to demonstrate improvement in the subject's quality of life. Assessments that evaluate the subject's functional vision may provide a better understanding of what users can actually do with the level of visual acuity measured in the clinical exam room. We recommend that you use the test procedures described below, as appropriate to your device.

Assessment of Orientation and Mobility

We recommend an orientation and mobility assessment of your subjects as measured by an independent trained orientation and mobility professional. The orientation and mobility professional should evaluate the functional visual ability of each implanted subject by observing the subject travel independently in real-world situations.

Assessment of Daily Living

Your protocol should include an assessment of daily living measured by an independent trained low-vision professional. The low-vision professional should evaluate the functional visual ability of each implanted subject by observing the subject perform daily self-care tasks such as dressing, grooming, cooking, and eating.

Quality of Life Questionnaire

Your protocol should include a validated low vision quality of life (QOL) questionnaire to assess the overall benefit of the retinal prosthesis when used in the home and other settings outside the clinic.

Spatial Mapping of Stimulated Visual Phosphene Fields

We recommend you conduct a careful assessment of the subject's phosphene "visual field" map when stimulating individual (or pairs) of stimulus array electrodes. For retinal prostheses with intraocular photosensors, we recommend projecting test spots directly onto the retinal implant. For a retinal prosthesis that relies on an external head or eyeglass mounted camera for visual input, we recommend generating a phosphene "visual fields" map while simultaneously monitoring the subject's implant eye and head position to account for movements during stimulation of individual electrodes. The protocol should include methods or devices to compensate for eye and head movements in perimetric tests mapping the subject's phosphene fields.

Form Vision Tests

To assess the ability of the prosthetic array to provide the implanted subject with timely form or pattern vision, we recommend short-duration, single letter or symbol recognition tests to avoid or minimize contamination by compensatory eye or camera movements.

Clinical Follow-Up for Visual Performance Assessment

Post-operative assessment of visual performance is critical to demonstrating a functional improvement of subject vision when using the implant. We recommend you provide a schedule of proposed post-operative clinical examinations of the subject's visual performance, ophthalmic exams for proper device position, and performance tests of implant electronics.

We recommend that you plan to follow subjects for three years or longer. We recommend you evaluate subject's visual performance at intervals of at most three months for the first year and at intervals of at most six months thereafter. It may be appropriate to submit your PMA application after collecting two years of follow-up data, depending on your device.

Long Range Clinical Study Considerations

You should enroll a sufficient initial number of subjects to submit long term data on a statistically significant number of subjects remaining after the number lost to follow-up. You should be prepared to address the possibility of post-approval studies that may continue 5-10 years after implantation (i.e., studies that FDA may require under 21 CFR 814.82(a)(2) as a condition of the approval of your future PMA application[15]). For

[15] See also the guidance entitled "Procedures for Handling Post-Approval Studies Imposed by PMA Order," available at http://www.fda.gov/cdrh/osb/guidance/1561.html.

studies that include long term follow-up, your IDE must include consent by all subjects to such follow-up (21 CFR 50.25(a)(1)), as explained below.

8. Informed Consent Document

Informed Consent Document

Your IDE application must include a copy all information to be provided to subjects to obtain informed consent (21 CFR 812.20(b)(11)). In your application we recommend that you explain your method of administering the informed consent documents (ICD), and how this method will account for the functional visual limitations of subjects enrolling in the study.

Your ICD must contain the elements specified in 21 CFR 50.25.

Required elements include, but are not limited to:

- a description of the procedures to be followed in the study (21 CFR 50.25(a)(1)),
- the expected duration of the subject's participation in the study, including any long term follow-up (21 CFR 50.25(a)(1)),
- a description of any reasonably foreseeable risks or discomforts to the patient, including surgical and postoperative risks and complications and short- and long-term risks and discomforts resulting from implantation of the prosthetic device and any associated electronics (21 CFR 50.25(a)(2)),
- a description of any benefit to the subject or to others which may reasonably be expected from the research (21 CFR 50.25(a)(3)), and
- any additional costs to the subject that may result from participation in the research (21 CFR 50.25(b)(3).

In addition, we recommend that an ICD for a retinal prosthesis describe:

- the frequency of subject tests required for the study,
- options for explantation should the subject be dissatisfied with the implanted device, and
- the need for periodic ocular health evaluations by an eye care professional beyond completion of the study, for as long as the implant remains in the eye.

9. Patient Information and Labeling

Your investigational plan must include copies of all labeling for the device. 21 CFR 812.25(f). Labeling of investigational medical devices must comply with 21 CFR 812.5. Among other requirements, the label must include the statement, "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use," and the label or other labeling must describe all relevant contraindications, hazards, adverse effects, interfering substances or

devices, warnings, and precautions (21 CFR 812.5(a)). See CDRH Device Advice, IDE Overview[16] for additional information about IDE labeling.

What follows is information specific to the labeling of investigational retinal prostheses.

Indications for Use

The labeling should be consistent with the indications for use statement that identifies the intended patient population. For these prosthetic devices, the target population should be a visually impaired disease population that may benefit from using the device.

Contraindications

The labeling must include information on all relevant contraindications (21 CFR 812.5(a)). Contraindications are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit. Contraindications may include retinal pathologies or prior damage to an element of the visual pathway, such as the optic nerve.

Warnings and Precautions

The labeling must describe all relevant hazards, adverse effects, interfering substances or devices, warnings, and precautions (21 CFR 812.5(a)). For example, your labeling must alert users to potentially injurious outcomes associated with use or misuse of the device and must describe actions users should take to avoid potentially injurious events. The precautions in your labeling should alert users to exercise special care for the proper use of the device. Depending on the device design or component composition, applicable warnings or precautions may include information about the compatibility of the device with various strength field MRI scanners, wireless devices, metal detectors, high voltage sources, and devices emitting strong magnetic fields. This information should include possible interactions with metal detectors, diathermy units, or cardiac defibrillators. Warnings or precautions about device use during specific activities such as walking, running, and swimming in specific environments may also be appropriate for some devices.

General Directions for Use

We recommend you include directions for preparation and use of the device and information about environmental conditions for storing the device, batteries, and any accessories.

Surgical Procedure

The labeling should describe steps to prepare or validate device functionality before implantation. We recommend you include a clear description of all device components, inserters, viewing devices, electronics, accessories, and surgical tools used for implantation. Labeling should also describe the implantation procedure itself. It should indicate that the procedure should be performed under sterile conditions in an operating room. It should specify, for example, the routes of entry, the incisions, the sutures and dressing, all drugs,

[16] http://www.fda.gov/cdrh/devadvice/ide/index.shtml

and all devices (such as the types and/or sizes of vitrectomy cannulae) used in the surgical procedure. It should describe any adverse events that can be anticipated to occur during the procedure, and how to prevent, manage, and/or mitigate them.

The labeling should further recommend use of a consistent medication regimen, including an anesthesia regimen, during the procedure and throughout the course of the study, as appropriate. Finally, it should describe the post-operative test procedures to verify implant integrity and proper placement.

We recommend that subjects' medication remain unaltered both before and during the clinical trial, other than those drugs prescribed in the clinical protocol for the post-operative recovery period. Additional surgery or medication used to treat unanticipated ocular conditions/complications should be recorded.

Accessory Devices

In addition, we recommend your labeling describe any accessory devices that are packaged with your device when no separate labeling for such accessory devices is available. For example, labeling should include a description of a surgical insertion or positioning device packaged with your device.

Subject Materials

In the IDE application, as part of the investigational plan, you should include items such as the subject user guide and implant card that will be provided to subjects.

Appendix A

Standards referenced in this document, available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm, include:

- ISO 15004-1,2 Ophthalmic instruments -- Fundamental requirements and test methods
- ISO 10939:1998 Ophthalmic instruments -- Slit-lamp microscopes
- ANSI RP27.1 standard: Photobiological Safety for Lamps and Lamp Systems-General Requirements.
- IEC 60601-1-2 Medical Electrical Equipment - Part 1: General Requirements for Safety; Electromagnetic Compatibility – Requirements and Tests (General).
- ANSI/AAMI/ISO 11134 - Sterilization of health care products-Requirements for validation and routine control of industrial moist heat sterilization
- ANSI/AAMI/ISO 11135 Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices
- ANSI/AAMI/ISO 10993-7 Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals
- ANSI/AAMI/ISO 11137 Sterilization of health care products - Radiation - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices
- ANSI/AAMI/ISO 11607 Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes, 1ed.
- ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing
- USP 30:2007, <85> Biological Tests and Assays, Bacterial Endotoxin Test (LAL)