Investigational Device Exemption (IDE) Guidance for Retinal Prostheses

Guidance for Industry and Food and Drug Administration Staff

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

Office of Science and Engineering Laboratories
Office of Device Evaluation

Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number 1809 to identify the guidance you are requesting.

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents 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 reviewers and members of industry who intend to submit an investigational device exemption (IDE) to the FDA to conduct feasibility and/or pivotal human clinical trials of their retinal prostheses in the United States to support a premarket approval (PMA) or a humanitarian device application (HDE).

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.

This device-specific guidance document should be considered in addition to other FDA publications on marketing or IDE applications and is not a replacement for those documents. The CDRH Device Advice website (http://www.fda.gov/http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm) has additional information about PMA (21 CFR 814), HDE (21 CFR Part 814 Subpart H), and IDE (21 CFR Part 812) submissions.
We recommend that you use this document as you develop data to support an IDE application. The pre-clinical and clinical tests mentioned in the guidance represent FDA's current thinking based on the information available at this time. Given the limited history with devices in this field, additional information may become available at a later date that suggests alternative test methods or functional assessments that may be more appropriate to assess the safety and effectiveness of retinal prostheses. For this reason, we strongly suggest the sponsors of such devices submit a Pre-Submission to facilitate discussion of clinical trial

designs, pre-clinical test protocols, and proposed indications for use for any specific retinal prosthesis.

This guidance cites a number of voluntary consensus standards which are recognized by FDA. You may access a list of the FDA-recognized standards from the CDRH web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. See Appendix A for a list of the voluntary standards referenced in this guidance. You may also consult FDA's guidance "Recognition and Use of Consensus Standards" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077274.htm).

For the purposes of this guidance, "you" refers to the sponsor of the IDE investigation and "we" refers to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 guidance means that something is suggested or recommended, but not required.

2. Scope

This document is limited to retinal prostheses, (i.e., visual prosthetic devices implanted on or beneath the retina, and those on or beneath the outer surface of the globe), that use electrical stimulation to provide some level of visual perception 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 primary mode of action of the product and in some circumstances may not be CDRH. For additional information on combination product jurisdiction or to submit a Request for Designation, please refer to the FDA Office of Combination Products (see http://www.fda.gov/oc/combination).

FDA believes that the devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m). Sponsors intending to use these devices in a clinical investigation in the United States must therefore submit an IDE application to FDA and obtain FDA and IRB approval of the application before beginning the investigation (21 CFR 812.20(a)). In addition to the requirement to obtain an FDA-approved IDE (21 CFR Part 812), sponsors of such studies must comply with the regulations governing institutional review boards (IRBs) (21 CFR Part 56) and informed consent (21 CFR Part 50).

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

c. Manufacturing Process

You should provide a description of the manufacturing and inspection steps related to achieving critical specifications for the device, including the final device acceptance criteria.

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

a. Table of Contents

We recommend you include a table of contents at the beginning of the submission 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 (std. dev.) of the test data.

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 IDE 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, you should provide detailed specifications for the formulation or chemical composition, particularly for materials with no history of intraocular or implant use. We recommend that you use generic names to describe the formulations of all device materials.

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

(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm). 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 evaluations, where applicable.

Bacterial Endotoxin Testing

We recommend that you provide bacterial endotoxin test results on implanted device components using a validated test method that includes inhibition and enhancement testing, such as USP 34:2011, <85> Bacterial Endotoxins Test, or AAMI ST72:2002/(R)2010, Bacterial endotoxins - Test methodologies, routine monitoring, and alternatives to batch testing.

Leachables Testing

We recommend that you determine the stability of the retinal prostheses material components in a saline environment through detection and quantification of possible degradation products from hydrolysis and changes in physical appearance. The test device should consist of the implant including all external material components (e.g., polymers, metals, ceramics, coatings, etc.) used in the construction of the finished device. Your extraction study should be designed to evaluate the stability of these materials in a saline environment at 35 °C for a period of at least five years or at an elevated temperature for a similar equivalent exposure. The saline media should be qualitatively and quantitatively analyzed at the end of the extraction for possible extractable components of the test material(s). The results should be evaluated to assess the risk for potentially harmful effects from the extractable components and they should be recorded in the device risk assessment.

Pyrogen Testing

The implant and its insertion devices should be tested for material-mediated pyrogenicity using the Rabbit Pyrogen Test (USP <151>) unless justification can be given. For device materials, firms should assess the risk of the presence of non-endotoxin pyrogens. See FDA's Guidance for Industry:Pyrogen and Endotoxins Testing: Questions and Answers (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm).

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 also 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 eye may be used for comparison. The animal study 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 24 hours. The animal may be sedated. After testing, you should perform a gross pathological and a detailed 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 6 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 2 weeks after implantation and again just before explantation to characterize the functionality of the device.

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 at a magnification sufficient to detect 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 capacitively coupled, charge-balanced or asymmetric, the charge recovery method 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 maximal pulse charge density, pulse frequency, and stimulus duration of the test.

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 the following 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 that you design the implanted components of your device to withstand a minimum of 5 years simulated use or provide a rationale for a shorter duration. We also recommend that 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. In addition, we recommend that you perform these tests at the maximal stimulation rate in a saline bath at 37^oC 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 assessment of device lifetime to the results of the tests conducted, which may include stress, hermeticity, corrosion, fatigue test analysis, and any other tests necessary to evaluate potential device failure modes. 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 also recommend you evaluate the hermeticity of your complete device using product lifetime immersion tests in a saline solution at 37^{o}C or higher. Tests that evaluate the items listed below may be done concurrently.

Evaluation of Coating Durability

For devices and associated cable assemblies coated with water-resistant films, we recommend you provide a study demonstrating that your coating remains effective after immersion testing. With coatings that are critical to device function, the test should be of a sufficient temperature and duration to detect coating failures. 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 and Bonding Patency Tests

We recommend that you validate the adequacy and reliability of any welding or bonding processes used in device fabrication, and their inspection methods. We also recommend you describe the inspection process of how device hermeticity of the case (if present) and cabling is validated and determined. Last, we recommend that 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^{o}C or higher.

- To assess surgical insertion stresses, we recommend that you demonstrate how your device and its cables will withstand surgical implantation, suturing, and any folding.
- We also recommend that you explain the clinical relevance of the loading conditions used for the accelerated flexion 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 design, thermal dissipation, electronic circuitry, ASIC, interconnects, cabling, and transmission coils of the implant.

Eye Orientation and Radio Frequency Link Safety

If the unit uses an external power source and signal, you should supply documentation showing that 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 electromagnetic interference (EMI) rejection filters, direct current leakage detection, recovery from power loss, electrode stimulation limits, error logs, hardware watchdogs and resets to validate proper device function.

Batteries

We recommend you describe the type of battery used in the device, its composition, location, 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 circuitry against inserting the battery with incorrect polarity or shorting.

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 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm)**.**

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 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 fail-safes,
- 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 (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf). 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 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm).

g. Visible and Electromagnetic Radiation, and Magnetic Resonance Imaging (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 15004-1,2:2007 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 RP27.1:2005 or- RP27.3:2007 standards: Recommended Practice for Photobiological Safety for Lamps and Lamp Systems-or equivalent.

Electromagnetic Compatibility

We recommend you evaluate your retinal prosthesis for compatibility with electromagnetic interference from various field strength 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 2: General Requirements for Safety; Electromagnetic Compatibility – Requirements and Tests (General) or an equivalent method. Also refer to "Electromagnetic Compatibility (EMC)" on FDA's website. (http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/ElectromagneticCompatibilityEMC/default.htm)

MRI Compatibility

We recommend that 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 that 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 that 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 in the as-manufactured state and over the stated shelf life. The device should also be demonstrated to withstand aging in its sterile package.

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.

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

- ANSI/AAMI/ISO 17665-1:2006 Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices.
- ANSI/AAMI/ISO 11135-1:2007 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 11137-1:2006/(R) 2010 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 11607-1-2:2006 Packaging for terminally sterilized medical devices – Parts 1 and 2.
- ASTM F1980-07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.
- AAMI/ANSI ST67:2003/(R) 2008 Sterilization of health care products - Requirements for products labeled "STERILE" 1st edition ST67:2003/(R).

7. Clinical Tests

We recommend you provide a written overview in your IDE application of all anticipated phases of the clinical investigation, outlining the studies you plan to conduct at each phase and describing any plans to pool data from more than one phase. Specifically, you should provide a detailed description of the initial feasibility study (i.e., study to refine clinical metrics or device design) and provide an overview of your later phase studies, if these studies are already in the planning stages. We recommend that you plan to follow subjects for three years or longer.

We recommend that surgery be performed only to implant the test device and not simultaneously correct other ocular conditions to avoid compromising demonstrations of clinical safety or effectiveness in your IDE studies. If device implantation will be performed simultaneously with other procedures because it is deemed necessary for patient safety and for the evaluation of the device, justification should be provided to account for potential confounding introduced by the second procedure in the analyses of the study endpoints.

a. Clinical Protocol

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 the final device design intended to support a marketing application.

For each planned clinical study we recommend you provide:

- the indications for use, which should include the target population,
- the study type [e.g., pivotal, expansion (continuation of a feasibility or pivotal study), 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 (sample size),
- the number of investigational sites, both inside and outside the U.S.,
- the subject inclusion and exclusion criteria including:
    - a defined age range for participants and the range of visual acuities and visual conditions considered acceptable for subject enrollment. A cognitive assessment is recommended in order to provide consideration for psychosocial factors such as subject coping/adjustment ability, family support, expectations of their participation, and ability to communicate and participate in all aspects of research.

  - other health-related conditions, medications, etc., that would confound study outcomes, or may be contraindicated for the proposed procedure resulting in exclusion from the study. We recommend that you document the reasons for not enrolling subjects who were screened under the protocol.

- primary safety and effectiveness endpoints described as specific objective clinical targets, and other endpoints such as optical evaluation of the placement of the electrode array near the retinal tissue.
- a study plan detailing tests and testing methodologies, and the stimulation range, rates, and levels you plan to test in the subjects.
  - Describe how you will sample (the number of repetitions and analysis) the subject's visual performance to adequately characterize pre-operative vision. This should be done at least three times total on three different days preoperatively. Post-operatively, the protocol should also include repeated measures to minimize variability in the assessments used to evaluate study endpoints.
  - All testing with the device should be done through a non-dilated pupil.
- a schedule/time table of all clinical tests to be performed for pre- and post-operative evaluation of the subjects. 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.
- the participating investigators, if known.

b. Unanticipated Adverse Device Effects

Investigators must report all unanticipated adverse device effects[1] to the sponsor and to their reviewing IRB's, in accordance with 21 CFR 812.150(a)(1). Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). When devising a list of "anticipated" adverse device effects for the protocol, the sponsor should consider that an event that would ordinarily be anticipated, but at a very low degree of incidence, should be considered unanticipated if it exceeded the expected degree of incidence. This is of particular concern in studies with a small number of

[1] Although the term "adverse events" is commonly used instead of "adverse effects," the latter term is the defined and used throughout 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), 21 CFR 812.140(b)(5), and 21 CFR 812.150(a)(1) & (b)(1).

subjects. Unanticipated adverse device effects could include, but are not limited to, the following: migration or extrusion of prosthesis, endophthalmitis, and electric shock.

We recommend that sponsors describe in their protocol any use of a Clinical Events Committee, a Data and Safety Monitoring Board, or a core laboratory. Sponsors must immediately conduct an evaluation of any unanticipated adverse device effects in accordance with 21 CFR 812.46(b). You 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).

c. Safety Outcomes

Other than for initial feasibility studies of limited enrollment, which usually involve fewer than 10 subjects, you should identify a primary safety endpoint in your protocol. You should also capture rates of surgical complications and potential longer-term adverse events. The choice of safety endpoint and list of potential adverse events will depend on the device design and the patient population for which the device will be indicated. A risk analysis should identify the most likely types of adverse events and also attempt to identify acceptable levels for the most probable and the most serious adverse events. The acceptable level of risk will depend upon the possible benefit and the level of visual function and health condition of the enrolled eyes. The statistical plan should justify the sample size based upon these safety considerations, in addition to providing justification based upon effectiveness.

One approach would be to base your primary safety endpoint in the protocol on adverse event rates obtained from the medical literature for similar surgical procedures, such that all events do not exceed a predetermined target rate. For certain small patient populations, such as those that would qualify the device as a Humanitarian Use Device, in order to support safety and probable benefit in a Humanitarian Device Exemption application, target rates may not need to be identified in the protocol, but instead the risk/benefit analysis performed at the study conclusion should characterize the expected rates for similar surgical procedures to provide only a frame of reference to which the safety performance of your investigative device can be compared.

d. Effectiveness Outcomes

Primary effectiveness endpoints of visual performance should provide quantitative documentation of implanted subjects' performance in support of device effectiveness. Depending on the patient population and the nature of the underlying condition, the effectiveness endpoints can be selected from the list of assessments below. Your IDE submission should include a rationale for the effectiveness endpoint(s) selected.

We recommend that the following effectiveness assessments be performed as appropriate to your device.

Assessments of Visual Function

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 also recommend you 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.

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. This should include two-point discrimination tests of the central electrodes in the stimulus array. 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 field" 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 Assessment

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

Assessments of Functional Vision and Patient Reported Outcomes

Assessments that evaluate the subject's functional vision may provide a better understanding of what users' visual capabilities are in real-world situations. Laboratory and contrived environments control the actual independent variables that are the source of visual problems for the visually impaired population. These independent variables include, but are not limited to glare, shadows, depth, variability in ambient light, weather conditions, etc. While laboratory assessments and contrived

environments may be acceptable for a non-pivotal study in which preliminary device effectiveness is to be evaluated, real world assessments should be used in pivotal studies. We recommend that you use the test procedures described below, as appropriate to your device.

Orientation and Mobility

We recommend an orientation and mobility assessment of your subjects' real-world performance as measured by an independent, trained orientation and mobility professional. An independent professional is not part of the company that manufactures and investigates the device. 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. This information cannot be statistically analyzed because the individual needs of each subject vary tremendously. The visual environments in which they exist and need to improve function will also vary significantly. This information will be used to corroborate objective findings such as visual acuity, visual fields, etc.

Activities 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, etc., as applicable.

Patient Reported Outcomes (PROs)

A PRO questionnaire should be administered to all subjects to assess the overall benefit of the retinal prosthesis when used in the home and other settings outside the clinic. The questionnaire should include questions regarding symptoms applicable to an implantable retinal prosthesis and its overall impact on health-related quality of life in low vision subjects. It is also recommended that depression be assessed as depression is often correlated to low-vision subjects. Subjects should be appropriately referred for further assessment and management as per their outcome on any measure of depression.

We recommend that a self-administered questionnaire be used to avoid bias.

The questionnaire items should have previously been referenced in the peer-reviewed literature and their reliability and validity undergone some degree of evaluation. FDA's **Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims** (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf) should be consulted for further guidance, particularly for evaluating the adequacy of a PRO instrument as a measure to support device claims, if the manufacturer wishes to make such claims. Investigators should be aware

that some devices will require the subjects to have vision rehabilitation training in order to assist them in the use of the device and the potential new vision it may afford them. In these instances, the PRO questionnaires will be an assessment of the training program more so than the device itself. In order to be an assessment of the device effectiveness, the questionnaire should be administered without rehabilitation training.

Some examples of existing questionnaires that measure the parameters listed above and can be used in combination are the short form of the National Eye Institute's Visual Function Questionnaire (VFQ-25) (impact on quality of life), Massof's Activity Inventory, Turano's Assessment of Mobility, The Melbourne Low Vision Index, VA VFQ-48, and the Patient Health Questionnaire (PHQ-9) (depression). Other possible scales for assessing depression include the GDS-15 (Geriatric Depression Scale) and Beck's Depression Scale (short form). The questionnaires used should be appropriately matched to the age range of subjects enrolled in the clinical investigation and should match the population being studied. For example, the MMPI (Minnesota MultiPhasic Personality Inventory) would not be suitable as a tool because it was based on a psychiatric prison population.

e. Statistical Analysis Plan

The protocol for a pivotal clinical study should include a statistical analysis plan (SAP). The SAP should describe how the study results will be analyzed and provide specific hypothesis tests and/or confidence intervals for analyses of primary and secondary endpoints of device safety and effectiveness. Effectiveness analyses should compare the outcomes for the active experimental device to the control condition (e.g., inactive device) or sham procedure control group. The SAP should include a sample size justification based upon the number of subjects needed to evaluate all primary effectiveness and safety outcomes, and important secondary outcomes. When testing multiple hypotheses, the plan should address how the overall Type I error rate will be preserved. Based upon your best estimate of expected loss to follow-up, you should adjust the number to be enrolled so that you have sufficient patient numbers at key time points. Your trial should be sized to address the possibility of continued follow-up 5-10 years after implantation for your clinical trial cohort (i.e., studies that FDA may require under 21 CFR 814.82(a)(2) as a condition of the approval of your future marketing application).[2] For studies that include long-term follow-up, your IDE must include consent by all subjects for such follow-up (21 CFR 50.25(a)(1)).In addition, post-approval studies enrolling new subjects may be required.

8. Informed Consent Document

[2] See also the guidance entitled "Procedures for Handling Post-Approval Studies Imposed by PMA Order," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm.

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 (21 CFR 50.25(a)(1)); this includes any long term follow-up,
- a description of any reasonably foreseeable risks or discomforts to the patient (21 CFR 50.25(a)(2)); this includes 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,
- 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. See CDRH Device Advice, IDE FAQs (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051480.htm) 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 coexisting 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. These warnings should also be reflected on the patient implant card.

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, and all devices (such as the types and/or sizes of vitrectomy cannulae) used in the surgical procedure. It should also 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 and feasible. Finally, it should describe the post-operative test procedures to verify implant integrity and proper placement.

To the degree possible, 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

List of Referenced Standards

For additional information about the Standards referenced in this document, please contact CDRH's Standards Program (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm) or by calling 301-796-6574.

ISO 15004-1 2006, Ophthalmic instruments - Fundamental requirements and test methods. - Part 1: General requirements applicable to all ophthalmic instruments.

ISO 15004-2: 2007, Ophthalmic Instruments - Fundamental requirements and test methods Part 2: Light hazard protection.

ISO 10939: 2007 Ophthalmic instruments - Slit-lamp microscopes.

ANSI RP27.1:2005, Recommended Practice for Photobiological Safety for Lamps and Lamp Systems. - General Requirements.

ANSI RP27.3:2007 Recommended Practice for Photobiological Safety for Lamps and Lamp Systems.- Risk Group Classification and Labeling.

IEC 60601-1-2:2001 "Medical Electrical Equipment – Part 1-2: General requirements for safety – Collateral standard: Electromagnetic compatibility – Requirements and tests".

ANSI/AAMI/ISO 10993-7 Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals Electromagnetic Compatibility – Requirements and Tests (General).

ANSI/AAMI/ISO 17665-1:2006 -Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices.

ANSI/AAMI/ISO 11135-1:2007 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 -1:2006/(R) 2010 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 11607-1:2006/(R) 2010 Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems, 3ed.

ANSI/AAMI/ISO 11607-2:2006/(R) 2010 Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes, 1ed.

ASTM F1980-07, Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.

USP 34:2011, <85> Biological Tests and Assays, Bacterial Endotoxin Test (LAL).

USP 34:2011, <151> Pyrogen Test (USP Rabbit Test).

AAMI ST72:2002/(R)2010, Bacterial endotoxins - Test methodologies, routine monitoring, and alternatives to batch testing.

ASTM F1980-07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

AAMI/ANSI ST67:2003/(R) 2008 Sterilization of health care products - Requirements for products labeled "STERILE" 1st edition ST67:2003/(R).