COVER PAGE

Clinical Protocol Title: Study of the Nucleus 24 and ABI541 Auditory Brainstem Implants (ABI) in Adult Non-Neurofibromatosis Type 2 Subjects

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Name of all sites (if applicable): Massachusetts Eye and Ear, 243 Charles St, Boston, MA 02114

IND/IDE number: G120214

Investigational drug(s) or device(s): Nucleus 24 and ABI541 Auditory Brainstem Implant Systems (Manufacturer: Cochlear Americas)

Regulatory Sponsor: Dr. Daniel J. Lee, Department of Otolaryngology, Mass. Eye and Ear, 243 Charles St., Boston, MA 02114

Funding Sponsor: None

Study Monitor

Medical Director: Dr. Daniel J. Lee

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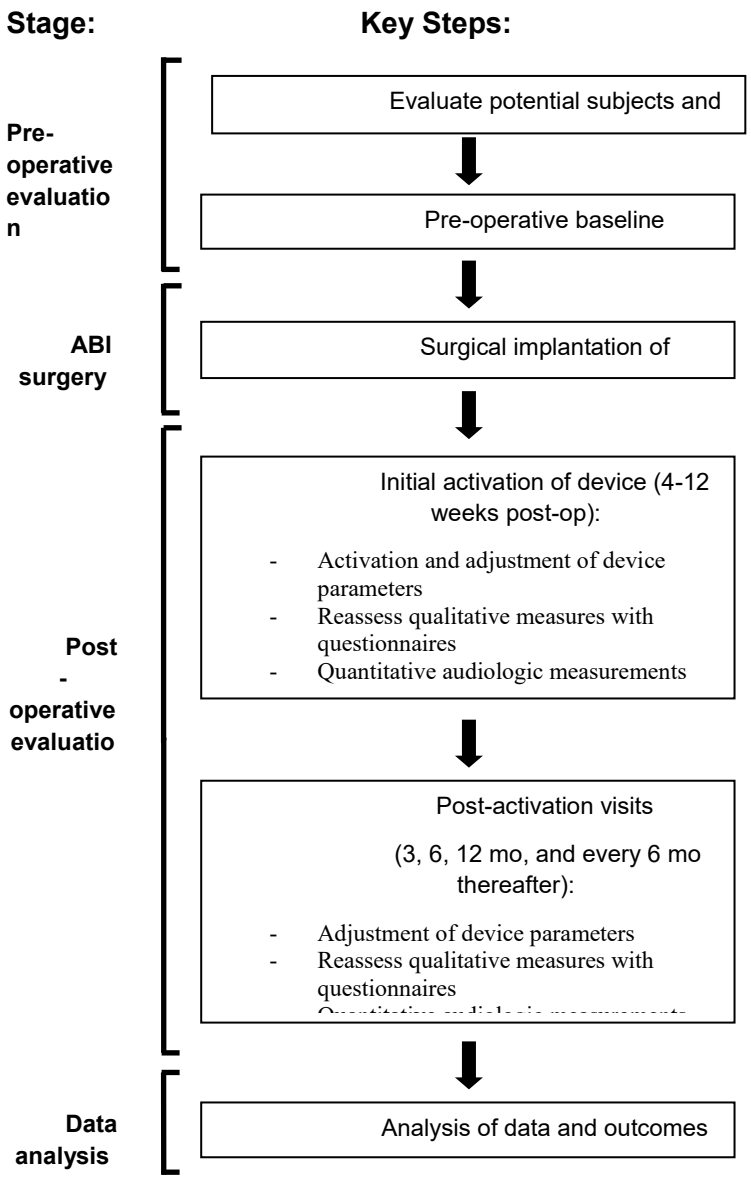
Clinical Laboratory(ies), Technical Department(s), and Institution(s) Providing Clinical Study Services: Mass. Eye and Ear, 243 Charles St., Boston, MA 02114

STUDY DESIGN SCHEMATIC



1. CLINICAL PROTOCOL

1.1 Background

Cochlear implants have been used for decades to improve hearing via direct stimulation of first order auditory neurons in the cochlea. CIs enhance hearing in the vast majority of users with either pre- and post-lingually deafness, and many CI recipients demonstrate open set word understanding. The auditory brainstem implant or ABI was first placed in a human adult patient 1979 in Los Angeles and is indicated for patients who are deaf and cannot receive a CI. The ABI bypasses the damaged or absent auditory nerve to stimulate the second-order neurons in the brainstem through placement of a surface electrode array on the cochlear nucleus (CN). Over 1000 pediatric and adult ABIs have been placed worldwide. Because ABI stimulation occurs further along the auditory pathway with activation of higher order neurons, this technology can take advantage of pathways that remain intact in patients with cochlear and retrocochlear pathology.

Our study aims to determine the efficacy of ABI in individuals with severe or profound hearing loss due to cochlear or retrocochlear anomalies distinct from NF2. In particular, base of skull/temporal bone fractures leading to VIIIth nerve avulsion, cochlear nerve agenesis or deficiency, cochlear aplasia, cochlear ossification, and auditory neuropathy prevent the faithful transmission of auditory information from the cochleae to the brainstem. These individuals do not benefit from hearing aids or CIs; however, there are cases where patients with these non-NF2 etiologies have greatly benefited from ABI placement.

The IDE Supplement for design change replaces the receiver / stimulator from the Nucleus ABI24M with the Nucleus ABI541. Both ABI devices feature a multichannel electrode lead that terminates in twenty-one, 0.7 mm platinum disk-electrodes. The 21

platinum contacts are arranged on the surface of a silicone rubber pad in three rows of seven contacts and are surgically placed on the surface of the brainstem; specifically, on the surface of the cochlear nucleus.

1.2 Rationale

The data supporting the clinical safety and efficacy of the Nucleus ABI24 in NF2 patients were provided to the FDA in March 2000, and later approved on July 21, 2000 unanimously for use by individuals with NF2. Other FDA criteria for ABI include age of 12 years or older, high motivation to participate in the rehabilitation process and appropriate patient expectations. Cochlear Americas subsequently received approval from the FDA in October 2000 (PMA No. P000015) for use of the ABI24 system in NF2 patients.

This proposed study aims to test the safety and clinical efficacy of the previously approved Nucleus ABI24 and new ABI541 systems in a small cohort of non-NF2 deaf patients, who are not candidates for or who have not benefited from CIs. Based on studies in Europe as well as at the University of North Carolina and House Ear Institute (University of California, Los Angeles), ABI placement in non-NF2 subjects leads to significant improvement in sound and speech recognitions skills (Colletti et al., 2001, Colletti et al., 2002, Colletti et al., 2004a, b, c, Colletti et al., 2005, Sanna et al., 2006, Sennaroglu et al., 2011, Grayeli et al, 2007). Enhanced auditory perception in non-NF2 patients with ABIs appears superior to ABI outcomes in NF2 patients, in part because the auditory pathways of non-NF2 patients have not been compromised. Indeed, based on these findings, several centers throughout the U.S. are now placing ABIs in non-NF2 patients as an off-label, non-FDA approved use of the Nucleus ABI24 system. We hope to complete a formal study examining the efficacy and safety of ABIs in non-NF2 patients. In particular, we will perform pre-operative, intra-operative, and post-operative physiological, psychophysical, and speech testing of non-NF2 patients who have undergone ABI surgery and thereby determine outcomes of ABI placement in this unique population of patients.

The Nucleus ABI24 has already been used safely and effectively in nontumor patients in prior studies completed in Europe and internationally (Colletti et al., 2010, Sennaroglu et al., 2009, Choi et al., 2011, Colletti et al., 2009). At MEEI, we are currently using the ABI24 system in NF2 patients safely and with good clinical outcomes, and importantly, the procedures for placement, activation, and management of the ABI24 device are identical in NF2 patients and the proposed cohort of non-NF2 patients. Thus, use of the ABI24 system in non-NF2 patients as part of our study will be safe and effective, even though this is an off-label use. Given that the stimulation methodology and electrode technology are unchanged in the new ABI541, the stimulation delivered by the ABI541 should be identical to that delivered by the ABI24M and should have the identical risks to the ABI24.

Subjects in our study will meet the basic criteria of being 18 years or older, medically and psychologically suitable ABI surgery candidates, up to date on meningitis vaccinations, and able to comply with study requirements. In addition, subjects will be chosen on the basis of cochlear or retrocochlear anomaly/pathology that interferes with transmission of auditory information from the cochleae to the brainstem, resulting in severe to profound bilateral deafness or conditions that cannot be treated otherwise, with conventional hearing aids or cochlear implants. If CI were previously used, subjects will have had a failed response, defined as ≤ 30% speech recognition and patient perception of inadequate benefit to continue using the device. Anticipated subjects include patients with bilaterally ossified cochleae (including a subgroup of recipients with failed response to previous CI), bilateral cochlear malformations leading to poor CI outcomes, bilateral temporal bone fractures, where the VIIIth cranial nerves have been disrupted, bilateral cochlear nerve agenesis, and those that are no CI candidates.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to better understand whether ABIs in non-NF2 patients may enhance hearing and sound detection in patients with severe to profound hearing loss. Out study will address several specific aims including:

Aim 1: Identification of ABI outcomes in non-NF2 patients – We will be testing the hypothesis that individuals with a range of conditions distinct from NF2 may benefit from the placement of an ABI. In particular, we will be exploring the performance of these patients in a battery of physiological, psychophysical, and speech-based tests including the Early Speech Perception Test, closed-set word recognition, and open-set word recognition with and without lip-reading cues. The performance of these patients will be compared to NF2 patients to better understand whether there are differences in these two patient groups.

Aim 2: Characterization of ABI parameters in non-NF2 patients – We will examine differences in electrode placement, stimulation selectivity, and modulation detection to test the hypothesis that non-NF2 patients have unique physiological ABI parameters compared to NF2 ABI patients. In addition, we will take advantage of intraoperative electrically evoked auditory brainstem responses to determine whether waves evoked during electrode placement intraoperatively are associated with auditory sensations postoperatively in non-NF2 patients.

Aim 3: Determination of ABI safety in non-NF2 patients – By carefully tracking post-operative outcomes following ABI placement in non-NF2 patients, we will test whether these patients have reduced major and minor complications compared to NF2 ABI patients.

2.2 Secondary Objective(s)

There are no secondary objectives of the proposed study.

3. STUDY DESIGN

3.1 Study Design Description

The study of the Nucleus ABI24 and ABI541 in non-NF2 patient will be conducted as a repeated-measure, single subject experiment with up to fifteen replications (goal of ten subjects, with 15 initially recruited to account for withdrawal or termination). A single subject research design in which each subject will serve as his or her own control will accommodate the heterogeneity of the subjects' background that is well known to influence auditory prosthesis outcomes and measures. Post-operative evaluations will be conducted at initial device activation, and three, six, and twelve months post-activation. Because the presence of absence of an ABI is easily recognized from visual inspection, blinding and masking procedures will not be utilized as part of the study design. The safety of the implant will be determined by monitoring major and minor complications in the cohort of study participants.

Pre-operative baseline measures will be obtained, including standard audiologic testing as described below.

Candidates that are suitable for surgery will undergo placement of an ABI. This surgery will utilize a translabyrinthine or retrosigmoid approach, depending on the anatomical and patient specific factors, to obtain access to the auditory nucleus of the brainstem. The electrode array of the ABI will then be placed and tested intra-operatively. After confirmation of optimal electrode array placement, the receiver will be implanted within the temporal bone posterior to the pinna. The patients overlying subcutaneous tissue and skin will then be closed and covered with dressings using standard surgical techniques.

Following surgical implantation of the Nucleus ~~ABI24~~ ABI541 and 4-12 weeks of healing, the device will be activated and auditory performance will be assessed as follows: at the time of activation and at three, six, and twelve months post-activation. Subjects will be evaluated with the prior approved Nucleus ~~ABI24~~ ABI541 speech processor programmed with an approved sound processing algorithm. Post-operative auditory function will be tested with a battery of psychophysical, speech perception, and lip-reading enhancement measurements.

The detailed list of post-operative assessments includes:

Initial Activation

Approximately 4-12 weeks post-operatively, subjects will be fitted with an approved Nucleus Sound Processor and initial stimulation will take place. The following procedures will occur at this visit:

- Modified Hearing Handicap Inventory, Dizziness Handicap Inventory, and Quality of Life (SF-36) questionnaires will be administered (see attached)
- Detection measures
- Speech perception and lip-reading enhancement measures
- Psychophysical measures
- Safety measures

Three, Six, and Twelve Months, and Biannual Post-activation Visits (for five years following ABI surgery):

The following procedures will occur at all these visits unless otherwise specified:

- Modified Hearing Handicap Inventory, Dizziness Handicap Inventory, and Quality of Life (SF-36) questionnaires will be administered (see attached)
- Detection measures at each post-activation interval

· Speech perception and lip-reading enhancement measures at each post-activation interval

· Psychophysical measures at each post-activation interval

· Safety measures at each post-activation interval

3.2 Allocation to Treatment

Because our study is a repeated-measure, single subject experimental design with up to fifteen replications, there is no proposed plan or procedure for allocating study participants to various cohorts of arms of the proposed clinical investigation.

4. SUBJECT SELECTION

4.1 Subject Inclusion Criteria

- 18 years of age or older
- English as the primary language
- Medically and psychologically suitable
- Willing to receive/have received meningitis vaccinations
- Able to comply with study requirements, including travel to the investigational site
- Cochlear or retrocochlear anomaly/pathology that interferes with transmission of auditory information from the cochleae to the brainstem, resulting in severe to profound bilateral deafness (thresholds of 90 dB or worse in both ears on pure tone audiometry and speech recognition scores ≤ 30% in both ears)
    - Conditions causing deafness that cannot be otherwise treated with conventional hearing aids or cochlear implants. If CI were previously used, subjects will have had a failed response, defined as ≤ 30% speech recognition and patient perception of inadequate benefit to continue using the device.
    - Expected subjects include those with:

- Bilaterally ossified cochleae (including a subgroup of recipients with failed response to previous CI)
- Bilateral cochlear malformations leading to poor CI outcomes
- Bilateral temporal bone fractures, where the VIIIth cranial nerves have been disrupted
- Bilateral cochlear nerve agenesis
- Not a CI candidate

4.2 Subject Exclusion Criteria

- Anomalies/pathology involving the brainstem or cortex
- Retrocochlear pathology resulting from NF2 or other types of cranial nerve or brainstem neoplasms or malignancies
- Co-existing medical conditions that require irradiation of the brainstem or auditory cortex
- Medical or psychological conditions that serve as contraindication to surgery
- Additional handicaps that would prevent or limit participation in evaluations
- Unrealistic patient or family expectations regarding the benefits, risks, and limitations inherent to the procedure and the prosthetic device
- Pregnant women

5. STUDY DRUG(S)/DEVICE(S)

5.1 Study Drug/Device Information

The Nucleus ABI24 system consists of a receiver/stimulator, a pocket sized speech processor worn on the body, and a microphone/headset. During surgery, the receiver/stimulator is implanted behind the ear. A wire leads from the receiver/stimulator to a series of 21 electrodes that are implanted in the auditory center of the brainstem, called the cochlear nucleus. The speech processor and microphone/headset pick up sound and transduce it into electrical impulses that are sent to the implanted receiver/stimulator. The impulse travels down the wire to the electrodes, which electrically stimulates the area that normally receives signaling from neurons of the ear.

The Nucleus ABI24 system is marketed under the brand name of Cochlear Nucleus 24 Multichannel Auditory Brainstem Implant and manufactured by Cochlear Americas (Engelwood, Colorado). In October 2000, the FDA approved use of the ABI24 system device in NF2 patients (PMA No. P000015).

Cochlear has developed a replacement for the ABI24M that uses the same electrode array as the existing ABI24M, but incorporates a more recent receiver/stimulator assembly. This device is referred to by Cochlear as the ABI541. The ABI541 is derived entirely from previous and existing approved products. The ABI541 uses the latest 500 series implanted receiver-stimulator, as is used in the current CI512 cochlear implant (approved in P970051/S116). This provides a slimmer electronics package for a reduced profile on the head and increased impact resistance in comparison to the ABI24M. The active electrode array is the same as used in the previously approved ABI24M.

5.2 Study Drug/Device Compliance/Adherence

Because the ABI~~24 system~~ is an implanted device, there are few concerns regarding compliance and adherence compared to most typical clinical trials. Our study is

designed as a repeated-measure, single subject experiment, and thus, each participant will serve as his or her own control. Throughout the study, we will confirm that subjects have been using the device through routine clinical follow-up and questionnaires at each appointment. Both qualitative and quantitative measures will be obtained to determine if subjects are benefiting from the ABI~~24 system~~, and the individual activation parameters at each visit will be compared to the prior visit to ensure that settings on the device have not been altered or changed between visits.

Although we anticipate that the vast majority of subjects will derive a safe and substantial clinical benefit from use of the ABI~~24 system~~, if a given subjects is non-compliant or non-adherent with use of the ABI~~24 system~~ or external sound processor, then we will collect a final set of qualitative and quantitative measures and simply follow their outcomes through routine clinical exams. This approach will allow for monitoring of any adverse safety or health concerns that may arise. Thus, no subjects in our study will be formally withdrawn for non-compliance or non-adherence and all study participants will be followed for five years after ABI surgery. If a subject chooses to withdraw from the study, they will be replaced by new study participants recruited from the clinic.

5.3 Study Drug Supplies

The Nucleus ABI24 system is already FDA-approved for use in NF2 patients. As with other cochlear and brainstem implants, the Nucleus ABI24 device is ordered prior to surgery. Notably, the Nucleus ABI24 device is already being used at MEEI in NF2 patients and standard preparation, dispensation, handling, and administration protocols are already in place. Similar protocols will be used in our study for the ABI541. In particular, upon receipt the device will be kept in storage with other electrical implant devices at MEEI, and at the time of surgery, dispensed/opened and subsequently handled with appropriate sterile technique. Thus, formulation and packaging, preparation and dispensation, and administration issues are either already addressed through current protocols or not applicable to our study.

5.4 Study Drug/Device-Storage and Accountability

The Nucleus ABI~~24 system~~541 is stored at room temperature upon receipt and kept securely until it is used during surgery. Given its electronic components, prolonged exposure to extreme temperatures should be avoided. In our study, the Nucleus ABI~~24 system~~ 541 will be kept in storage with other electrical implant devices at MEEI, and at the time of surgery, dispensed/opened and subsequently handled with appropriate sterile technique. Nearly all aspects of the device are implanted in the patient (with the exception of the speech processor and microphone/headset, which are worn externally). The device contains a few disposable components, which are primarily used to accurately place the device intra-operatively. These components will be disposed of in biological waste containers during the surgery. Because the ABI~~24 system~~ is an implanted device, protocols for the proper destruction or disposition of study devices upon completion or termination of the clinical research are not necessary.

5.5 Other Medications

Out study does not include the planned us of other medications concomitantly with the ~~Nucleus~~ ABI~~24 system~~ device. If patients experience complications or medical concerns related to the ~~Nucleus~~ ABI~~24 system~~, these will be handled appropriately through routine medical management in the Otology clinic or appropriate referral to other providers. There are no specific medications that are not allowed in participants of our clinical research study. In addition, rescue medication or therapies will not be used in this study.

6. BIOSPECIMEN COLLECTION (IF APPLICABLE)

Biospecimens will not be collected as part of our study. Thus, specimen, preparation, handling, shipping and other aspects of specimen management are not applicable.

6.1 Specimen preparation, handling, and shipping

N/A

6.2 Instruction for specimen preparation, handling and storage

N/A

6.3 Specimen shipment

N/A

6.4 Future use of stored specimens

N/A

7. STUDY PROCEDURES

7.1 Screening Procedures

After confirming that potential study participants meet basic demographic inclusion criteria, patients will be evaluated by a trained Otologist at MEEI. A detailed history will be obtained and physical exam will be completed. Subjects will also be evaluated for baseline qualitative measures using questionnaires and quantitative

measures using audiologic testing. In particular, audiometric threshold testing and Auditory Evoked Potential testing will be completed to confirm acoustic auditory status. These parameters will be compared to inclusion criteria to determine if a subject meets all inclusion criteria and represents a viable candidate for ABI surgery.

7.2 Enrollment/Baseline Procedures

All baseline procedures will be completed at the time of screening. This includes qualitative measurement using the Modified Hearing Handicap Inventory, Dizziness Handicap Inventory, and Quality of Life (SF-36) questionnaires as well as audiologic tests such as standard audiometric threshold and Auditory Evoked Potential testing.

7.3 Study Drug or Device Procedures

Subjects will undergo pre-operative evaluation for ABI surgery. Those subjects that are appropriate for surgery will undergo a procedure for implantation of the ABI~~24 system~~541. As per manufacturer protocol, the parameters of the ABI~~24 system~~541 including adjustment of electrode sensitivities and activation of specific electrodes will be completed at each follow-up visit post-operatively. This process involves adjustment of device parameters by a trained audiologist who subsequently administers audiologic tests to confirm optimal activation of the ABI~~24 system~~541.

7.4 Standard of Care Procedures

All audiologic testing and assessments represent the standard of care. Aspects of our study that go beyond routine standard of care are outlined above and in the informed consent.

7.5 Follow-up Procedures (Incorporate only if follow-up procedures will be performed)

Study participants will have audiologic testing and device activation and adjustment completed at follow-up appointments. These post-operative follow-up

appointments will occur at 4-12 weeks, three, six, and twelve months, and biannually thereafter until the study end point of five years. Timing of these appointments may vary by as much as four weeks prior to or after the planned follow-up date (e.g. between 2-4 months for the 3 month follow-up).

7.6 Unscheduled Visits

Unscheduled visits will be taken in the Otology clinic as needed to address any concerns study participants may have regarding the use of their Nucleus ABI~~24 system~~541 device.

7.7 Early Termination

Subjects whose participation in the study is terminated early will be replaced through the recruitment of additional subjects through Otology clinic. All subjects may voluntarily withdraw from the study at any time.

7.8 Schedule of Activities (Study Table)

Please see the study grid included in the IRB application.

8. SAFETY AND EFFECTIVENESS ASSESSMENTS

8.1 Safety Assessments

Safety assessments will include complications questionnaires and frequent post-operative follow-up visits. Inquiries about both major and minor complications will be made and any complications will be recorded. A research assistant will regularly review safety measures every month for all study participants and discuss any safety concerns/adverse outcomes with the investigator.

Any reported safety issues will be carefully recorded and following completion of the study, safety outcomes will be analyzed. Any unanticipated adverse events will be reported to the HSC, FDA, and Cochlear Americas (see Section 9).

8.2 Effectiveness Assessments

Effectiveness assessments will be completed based on audiologic testing and subjective questionnaires at each follow-up appointment. These will be compared to the subjects pre-operative baseline measures. In particular, primary dependent measures will include:

- Speech Perception and Lip-reading Enhancement Measures
    1. Monosyllable/Trochee/Spondee Test (MTS), presented via live voice
    2. CUNY Sentences, presented via video laserdisc in the sound-alone, vision alone, and sound-plus vision conditions

- Detection Measures
    3. Aided (ABI) Sound Field Thresholds measured at octave intervals from 250 to 6000 Hz inclusively.

- Psychophysical Measures
    4. Electrical Thresholds Measured in Current Level
    5. Electrical Maximum Comfort Levels Measure in Current Level
    6. Pitch scaling

- Subjective Questionnaires
    7. Hearing Handicap Inventory
    8. Dizziness Handicap Inventory
    9. Quality of Life (SF-36) questionnaire

9. ADVERSE EVENT RECORDING AND REPORTING

9.1 Recording Requirements

Research subjects will be routinely questioned about adverse events at study follow-up visits.

- **RECORDING REQUIREMENT**

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of suspected causal relationship to the study device will be recorded in the subjects' case histories (source data, case report form). For all adverse events, sufficient information will be obtained to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the casual relationship between the adverse event and the ABI~~24 system~~.

Adverse events or abnormal test findings felt to be associated with the ABI~~24 system~~ will be followed until the event (or its sequel) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

- **ABNORMAL TEST FINDINGS**

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
- The test finding leads to discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the Sponsor-Investigator of the IND or IDE application
- Of note, simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- **CASUALTY AND SEVERITY ASSESMENT**

The Sponsor-Investigator of the IND or IDE application will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the ABI~~24 system~~541; and 3) if the adverse event meets the criteria for a serious adverse event.

If the Sponsor-Investigator's final determination of causality is "unknown and of questionable relationship to the study device", the adverse event will be classified as associated with the use of the ABI~~24 system~~541 for reporting purposes. If the Sponsor-Investigator's final determination of causality is "unknown but not related to the study device," this determination and the rationale for the determination will be documented in the respective subject's case history (case report form).

9.2 REPORTING PROCEDURES

- **REPORTING OF ADVERSE REACTIONS TO FDA**
  - Written IND Safety Reports (if applicable)
  - Telephoned IND Safety Reports – Fatal or life-threatening suspected adverse reactions

- **Reporting Adverse Events to Other External Entities**

  Adverse event reports will also be submitted to the Cochlear Americas, which has provided a Right of Reference Letter for the Nucleus ABI~~24 system~~541, in accordance with their respective reporting guidelines.

- **Reporting Adverse Events to the Human Studies Committee (Please follow HSC Policy "REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS")**

  1. Reporting of Unexpected and Related/Possibly Related Events

Serious Adverse Event (SAE)

Any serious adverse event will be reported to the HSC. These SAE include those that both (i) are unexpected and related/possibly related to research; and (ii) occur while the subject is enrolled in the study or that occur within 30 days of the conclusion of the subject's participation in the study, of which the PI or study staff become aware. In order to determine whether a specific adverse event is unexpected, the PI will consider whether the event is consistent with the risks described in the protocol-related documents (e.g. protocol, consent form, Investigator's Brochure). In order to determine whether a specific adverse event is related or possibly related to subject's participation in the research, the PI will consider the temporal relationship between the event and the investigational product being studied or study procedure. If an adverse event is at least partially caused by the procedures and /or investigational products, it will be considered related/possibly related to research.

Any adverse events that are serious, unexpected and related or possibly related to the study will be reported to the HSC within 7 calendar days from the time the PI becomes aware of the event. Any unexpected and study-related death will be reported to HSC within 24 hours of the PI's knowledge of the event by e-mail or telephone. A completed AE report form will be submitted to HSC within 7 calendar days of initial HSC notification. If the PI becomes aware more than 30 days after the conclusion of a subject's participation of a serious adverse event that is both related to the research and unexpected, the PI will report the event to HSC at the time he/she becomes aware of it.

Non-Serious Adverse Event

All non-serious adverse events that are unexpected and related or possibly related to the research will be reported to the HSC within 30 calendar days from the time the PI becomes aware of the event.

2. Reporting of Expected and Related/Possibly Related Events

The PI will submit a summary report to the HSC for all serious and non-serious events that are expected and related/possibly related to the study at the time of continuing review.

3. Reporting of Unanticipated Problems

The PI will promptly report to the HSC Unanticipated Problems (UAPs) involving risks to subjects or others. In order to determine whether a specific problem constitutes a UAP, the PI will consider the following:

- The vast majority of adverse events occurring in human subjects do not represent UAP because most AEs are expected in the context of known toxicities or side effects of the research procedures and/or are due to the natural history of subjects' underlying diseases and conditions;
- a small proportion of AEs do represent UAPs; and
- UAPs may include events that are not adverse events.

All UAPs involving risks to subjects or others will be reported in writing to the HSC within 7 calendar days from the time the PI becomes aware of the event. If a UAP or an unexpected SAE results in a subject's death or was potentially life-threatening, the PI will notify HSC through e-mail or phone within 24 hours from the time the event is identified. A follow-up report will be submitted at a later date when more information is available. The PI will notify HSC through e-mail or phone within 24 hours from the time the event is identified for UAPs that take the form of a data loss.

9.3 Withdrawal of Subjects due to Adverse Events

Subjects experiencing major adverse events will be referred for appropriate care as needed. The severity of adverse events will be determined by the investigator in consultation with the HSC. Briefly, events that lead to irreversible or permanent disability of the patient will be considered serious and the subject will be reminded that participation in the study is voluntary and that withdrawal is possible at any time. If the subject remains interested in continuing to participate in the study, then after receiving the appropriate care, data will continue to be collected from the subject at follow-up visits as described in the study design. Medical attention and follow-up for any adverse events will continue until the adverse health concern has resolved or if not, then continued indefinitely. If a subject is withdrawn from the study due to an adverse event, they will be replaced by recruiting a new study participant from clinic.

10. STATISTICAL METHODS/DATA ANALYIS

10.1 Primary endpoint(s) or outcome measure (s)

The study has a primary endpoint of five years following ABI surgery for up to fifteen study participants. Outcomes measures include audiologic measures and subjective questionnaires as described in previous sections, as well as safety assessments completed throughout the study.

Our previous work has established the importance of these physiological, psychophysical, speech tests, questionnaires on efficacy, and safety measures as a comprehensive method for assessing the outcomes of ABI surgery in non-NF2 patients. In particular, using these measures we can obtain both objective and subjective data to assess the safety and efficacy of ABI placement in non-NF2 patients and thereby understand how ABI placement has influenced patients' hearing and quality of life. In addition, by comparing our findings and measures to data obtained in other patient populations such as NF2 patients, we will better understand whether ABI placement in non-NF2 patients has improved safety and efficacy compared to ABIs in other patient populations.

10.2 Secondary endpoints or outcome measure (s)

There are no secondary endpoints or outcome measures for this study.

10.3 Sample Size Determination

Our study will recruit fifteen participants for placement of a Nucleus ABI~~24 system~~541 device with follow-up measurements and assessments for five years post-operatively. Although our study is limited to a small sample size of up to fifteen patients, the single subject research design will allow each subject to serve as his or her own control, accommodating heterogeneity of the subjects' backgrounds and providing adequate power to test the major hypotheses. Previous studies have used a similar study design and sample size, with statistically significant findings regarding efficacy and safety of ABIs in non-NF2 patients.

10.4 Analysis Population (if applicable)

Given the small sample size of up to fifteen patient for our study, we will plan to analyze data obtained from all participants. If a subject withdraws from the study, data obtained from their participation in the study will still be incorporated into outcomes and safety analyses.

10.5 Effectiveness Analysis (if applicable)

As this study is a single-subject research design, Nucleus ABI~~24 system~~541 effectiveness results will be analyzed for each subject individually. The data will be described using conventional descriptive statistics. Data analyses will be conducted using appropriate non-parametric statistical tests. When CI performance data from the same ear are available in a subject or can be obtained prior to ABI placement, comparisons with subsequent ABI performance will be generated. In addition, outcomes from non-NF2 patients enrolled in the current study will be compared to data collected in previous outcomes of the Nucleus ABI24 in NF2 patients using standard statistical tests. For all statistical analyses, a $p \leq 0.05$ level of significance

will be used. Any subsequent deviations from the statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to this application.

10.6 Safety Analysis

As this study is a single-subject research design, Nucleus ABI~~24 system~~541 safety results will be analyzed for each subject individually. The data will be described using conventional descriptive statistics. Data analyses will be conducted using appropriate non-parametric statistical tests. Safety outcomes from non-NF2 patients enrolled in the current study will be compared to data collected in previous analyses of the Nucleus ABI~~24 system~~541 in NF2 patients using standard statistical tests. For all statistical analyses, a $p \leq 0.05$ level of significance will be used. Any subsequent deviations from the statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to this application.

10.7 Interim Analysis

Interim analysis will be completed once three, five, and eight patients are enrolled. These analyses will be completed at one and three years post-operatively for each of these cohorts. Interim analysis will be performed by study staff and the Investigator and results will be shared with the HSC through routine study renewal forms. If significant concerns arise regarding safety of the proposed device, these analyses will be shared with the HSC within 7 days and appropriate discussion to follow. Of note, the safety concerns described here do not include adverse or unanticipated safety events, which will be handled as described in Section 9.

10.8 Data and Safety Monitoring

All persons working on the study will be briefed by the investigator or other leaders of the trial regarding their role in the study and appropriate data management and safety monitoring procedures. During these meetings, the ABI device as well as individual trial-related duties and functions will be discussed. The investigator or other leaders of the study will provide an opportunity for all persons assisting with the

trial to ask questions and clarify the protocol and their individual role. Each individual will be required to read the study protocol and acknowledge that they have read and understand the protocol along with their trial related duties and functions.

The investigator and study staff will monitor the validity and integrity of the data and any safety concerns as well as adherence to the IRB-approved protocol through regular biweekly or monthly meetings in which collected data is shared, new analyses are discussed, and any issues with protocol adherence are reviewed.

A research assistant will be responsible for monitoring the study, including obtaining source documents, organizing completed informed consent forms, reviewing the accuracy and completeness of case report forms, and managing the protocol timeline to ensure that all assessments are appropriately administered and collected from study participants.

12. DATA HANDLING AND RECORD-KEEPING

12.1 Data Recording and Record-Keeping

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The Sponsor-Investigator will review, approve and sign/date each completed CRF; the Sponsor-Investigator's signature serving as attestation of the Sponsor-Investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Clinical data that may be recorded directly on the CRF include: subjective report of symptoms, audiologic measures, lab values, and physical exam findings. Any missed, unused, or spurious data will be reviewed by the Investigator and followed up by study personnel. Subject specific data and Case Report Forms will be coded with a numeric random identifier, with information regarding which codes correspond to which

subjects stored on secure information systems at Mass. Eye and Ear. Electronic systems used are in compliance with FDA electronic records and signature regulations.

14. STUDY DISCONTINUATION CRITERIA

14.1 Discontinuation of Individual Research Subjects

As described, safety measures will include complications questionnaires and frequent post-operative follow-up visits. Inquiries about both major and minor complications will be made and any complications will be recorded. A research assistant will regularly review safety measures every month for all study participants and discuss any safety concerns/adverse outcomes with the investigator. The investigator will then decide whether the research study should be altered or stopped. If a clear answer is not evident, the investigator will discuss the safety concern with the Human Studies Committee and make appropriate adjustments to the study as needed. Other discontinuation criteria are described under Section 5.2 (Withdrawal of subjects due to non-compliance/adherence) and section 9.3 (Withdrawal of subjects due to adverse events) of the clinical protocol.

If withdrawn subjects are agreeable to measurements of clinical outcomes and assessments of device safety, these data will be collected until five years following ABI surgery. As with other criteria for withdrawal, subjects that are withdrawn will be replaced through recruitment of additional study participants in clinic.

14.2 Sponsor-Investigator Discontinuation of the Clinical Research Study

At this time, the sponsor-investigator has no known criteria for discontinuation of the clinical research study. Any protocol modifications will be submitted prospectively to the HSC and to the FDA for discontinuation of parts of the clinical study. If portions of the study must be discontinued, the HSC and the FDA will be notified promptly of discontinuation, including which portions of the study (if any) remain. In addition, enrolled subjects will be notified at follow-up appointments or by phone of discontinuation of any aspects of the study. If parts of the clinical study are

discontinued, a revised informed consent will be discussed and obtained from subjects for continued participation in the study. All study staff and sub-investigators will be notified directly by the investigator of discontinuation of parts or all of the clinical research study. Because all audiologic measurements and safety assessments in this study are part of normal routine follow-up after ABI surgery, these measures will continue to be obtained following discontinuation of the study through normally scheduled follow-up appointments. However, subjective questionnaires will not be administered to subjects following discontinuation of the study.