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**COVER PAGE**

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**Clinical Protocol Title:** Cochlear Implantation for treatment of Single-Sided Deafness

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MED-EL MAESTRO Cochlear Implant with Flex 28 electrode array

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**Study Monitor**

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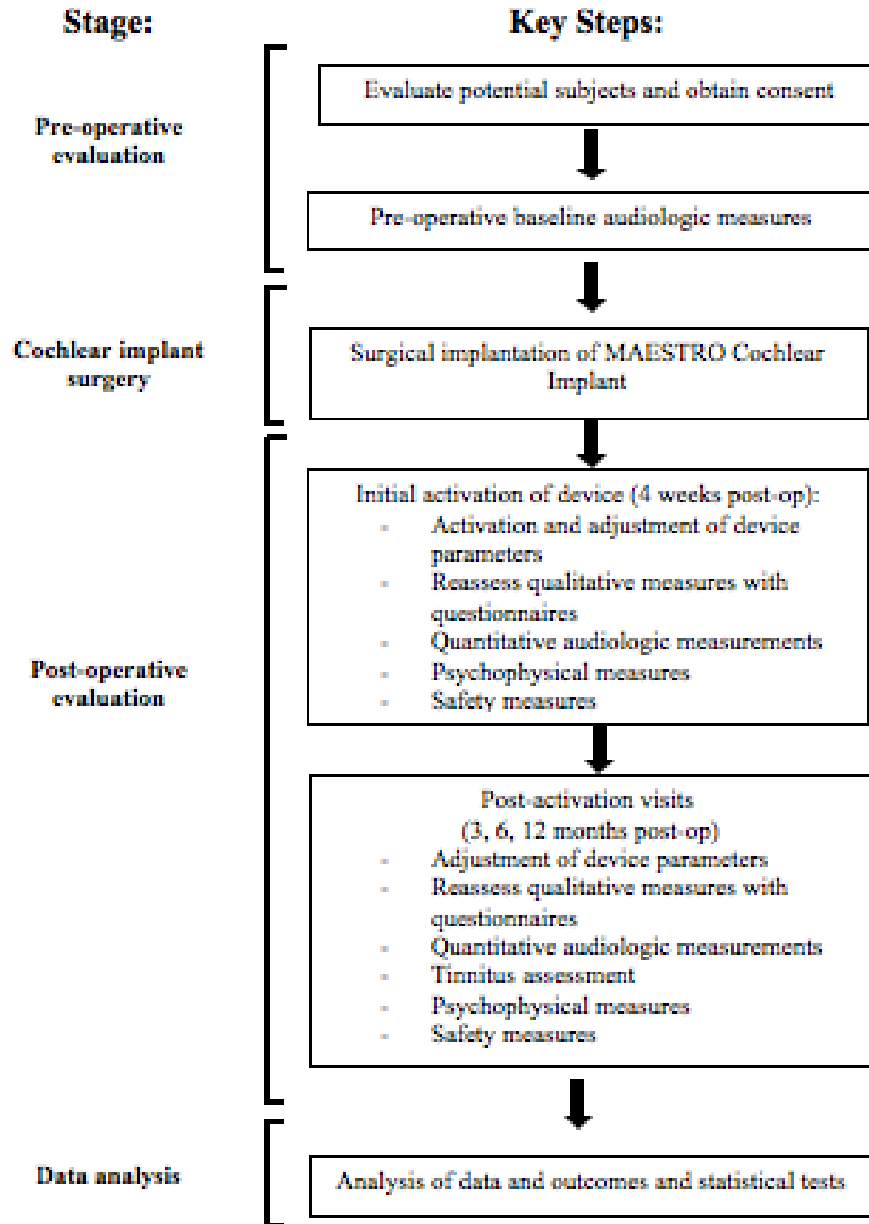
Massachusetts Eye and Ear Infirmary Department of Audiology

University of Wisconsin Department of Communication Disorders

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STUDY DESIGN SCHEMATIC

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## 1. CLINICAL PROTOCOL

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### 1.1 Background

Our study aims to determine the efficacy of the MAESTRO Cochlear Implant in patients with postlingual, single-sided deafness. Single-sided deafness can arise from base of skull/temporal bone fractures leading to hearing loss, infection such as meningitis or labyrinthitis, vascular disease affecting the inner ear, Ménière's disease, or sudden sensorineural hearing loss, each of which prevents the faithful transmission of auditory information from the cochlea to the brainstem. Patients with single-sided deafness may also suffer from tinnitus in the affected ear, which can be debilitating. Unlike current treatments for single sided deafness, cochlear implantation has the potential to improve hearing abilities and suppress tinnitus in these patients.

Many patients with single-sided deafness experience difficulty hearing in the setting of background noise, impaired sound localization and tinnitus. These symptoms can affect communication in social settings, causing psychosocial stress and resulting in a decreased quality of life. Treatment options for single sided deafness in the United States include the contralateral routing of signals (CROS) hearing aid and the implantable bone conduction hearing aid. These devices take sound from the affected ear and transmit it to the unaffected ear. Although these options can improve sound and speech awareness on the deaf side, studies have shown that use of these devices does not significantly improve sound localization and does not address the issue of tinnitus in the deaf ear. Recently, several European studies have shown that cochlear implantation can improve both perceived hearing ability and measured speech comprehension and localization in adult and pediatric patients with unilateral hearing loss. Furthermore, many patients experience tinnitus suppression following cochlear implantation. These clinical data suggest that cochlear implantation provides clinical benefits not seen with the CROS or bone-conduction devices.

## **1.2 Rationale**

Single-sided deafness (SSD) afflicts approximately 60,000 new patients per year in the United States (Popelka et al., 2010). The most common causes of these single-sided losses are sudden sensorineural hearing loss, Ménière's disease, trauma, infections, and vascular insults. Patients with SSD face significant difficulty with sound localization and communicating in the presence of background noise (Bishop and Eby, 2010; Kamal et al., 2012). Tinnitus is another significant problem for some SSD patients; this can be incapacitating and no available effective therapies exist outside of cochlear implantation (Arts et al., 2012). Difficulty hearing in background noise and increased tinnitus can lead to significant frustration in social situations and contribute to increased isolation and a decreased quality of life.

In the United States, options to treat SSD have included contralateral routing of signals to the hearing ear via (CROS) hearing aids and the bone-anchored hearing aid (BAHA) system, an osseointegrated device that provides direct transcranial stimulation of the contralateral side. For SSD, the BAHA appears to outperform other types of CROS aids (Niparko et al., 2003). Indeed, the BAHA provides some benefit to SSD patients, as measured both by subjective patient reports and an improvement on hearing-in-noise tests. However, these aids are unable to provide information regarding sound localization, even after long-term use (Nicolas et al., 2012; Snapp et al., 2012; Linstrom et al., 2009; Niparko et al., 2003). SSD patients using the BAHA do, moreover, continue to suffer significant deficits on hearing-in-noise testing relative to normal hearing adults (Linstrom et al., 2009). Taken as a whole, data supporting the use of the BAHA in SSD suggest that while SSD patients derive some benefit from the device, this benefit is limited.

Tinnitus is another problem experienced by a significant fraction of SSD patients. While the precise neural substrates of tinnitus remain to be elucidated, hearing loss is highly correlated with the development of ipsilateral tinnitus. Current treatment strategies for tinnitus involve cognitive behavioral therapy in conjunction with optimization of aural inputs (Arts et al., 2012) and, in some cases, antidepressant therapy. As SSD patients have by definition lost useful hearing on one side, optimizing input on that side is not useful. The treatment of tinnitus in SSD patients has therefore been limited to helping these patients deal with the symptom rather than addressing the root cause of the problem.

To directly address the tinnitus experienced by SSD patients by increasing signal through the cochlear nerve, several groups have carried out cochlear implantation (Arts et al., 2012). These results have been promising, with 80-95% of patients in the largest series finding improvement in their tinnitus or even, in a fraction of cases, complete tinnitus suppression. In nearly all cases, this effect is dependent on signal from the cochlear implant, supporting the idea that decreased input from the cochlear nerve contributes to the development of tinnitus (Van de Heyning et al., 2008; Arndt et al., 2010; Ramos et al., Kleine Punte et al., 2011).

Cochlear implantation in SSD patients has also resulted in significantly improved sound localization and ability to hear in noise (Kamal et al., 2013). One important study examined SSD patients who were treated with cochlear implantation; the untreated side was either normal or treated with a hearing aid. The data demonstrated that, although there was a significant benefit in speech understanding and subjective quality of sound, sound localization only improved in patients with normal hearing on the opposite side (Vermeire and Van de Heyning, 2009). These findings are consistent with a more recent pilot study, in which three patients with short-term SSD and normal hearing in the other ear received a cochlear implant on the deafened side. These patients all achieved open-set speech recognition, improved sound localization, and improved word recognition in noise (Firszt et al., 2012). Another critical study evaluated SSD patients who had undergone cochlear implantation, comparing use of the cochlear implant to a CROS or BAHA. This study found that cochlear implantation resulted in significant gains with respect to objective sound localization and hearing-in-noise testing relative to the CROS or BAHA device in the same patients. Subjective and quality of life measures were also significantly improved with use of the implant (Arndt et al., 2010). Taken together, early data indicate that cochlear implantation in SSD can result in significant tinnitus suppression, improved sound localization and hearing-in-noise, and better quality of life overall.

- 2 Our hypotheses are that adult patients with postlingual, single-sided deafness who undergo cochlear implantation will 1) wear the implant full-time, 2) report that the cochlear implant provides benefit, 3) show improvement in speech comprehension in quiet and in background noise, 4) demonstrate an improvement in sound localization, and 5) report a reduction in the frequency and intensity of tinnitus compared to before

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surgery. To test these hypotheses, we will formally and systematically test patients both before and after surgery as detailed below.



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## 2. STUDY OBJECTIVES

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### 2.1 Primary Objective

The primary objective of this study is to better assess the efficacy of cochlear implants in enhancing hearing abilities in patients with single sided deafness. The parameters being assessed include hearing in background noise, sound localization, tinnitus suppression, and overall quality of life. Our study will address several specific aims including:

**Aim 1: Determine the audiologic outcomes following CI surgery for single sided deafness.**

We will implant ten adult patients with postlingual single sided deafness with the MED-EL MAESTRO CI with Flex 28 electrode array using a round window insertion approach. Intraoperative imaging with a reverse Stenver xray will be performed to confirm proper electrode placement. We will assess sound-field thresholds for the cochlear implant alone and word recognition ability in the monaural and binaural condition. . We will also have patients complete the following questionnaires: 1) Hearing Handicap Inventory for adults, 2) Abbreviated Profile of Hearing Aid Benefit and 3) Speech, Spatial, and Qualities of Hearing Scale (SSQ)(Noble and Gatehouse, 2006) prior to and after implantation to assess subjective benefit outcomes. Finally, we will document the reported frequency of implant use and the use settings of the implant.

**Aim 2: Determine the spatial hearing benefits following CI surgery for single sided deafness.**

The bilateral benefits of understanding speech-in-noise will be evaluated in collaboration with Dr. Ruth Litovsky at the University of Wisconsin. Briefly, subjects will be flown to Madison and undergo spatial hearing testing in Dr. Litovsky's lab pre- and post-operatively. Funding from Dr. Litovsky's lab will cover all costs for travel, accommodations and meals for the subject and one travel companion. Subjects will be their own control and testing will take place at time points before and after surgery. They will be tested with the acoustic ear alone before the CI surgery. Following CI surgery, testing will be done with the bilateral condition and with the acoustic ear alone. On one task, subjects will identify a single

word randomly chosen from a set of fifty possible alternatives and presented from a loudspeaker directly in front of the subject. Speech intelligibility will be tested by masking sentences co-presented at different spatial configurations ( $-90^{\circ}$  or  $+90^{\circ}$ ). The presentation level of the target speech will be varied in order to generate different signal-to-noise-ratios at each condition. We will evaluate implanted SSD patients with the device turned on and off to directly evaluate the contribution of the cochlear implant to understanding speech-in-noise. On a second task, we will evaluate sound localization in a 19-loudspeaker array. Stimuli are brief speech sounds; the overall level is roved and the spectrum is roved within a critical band to eliminate monaural level and spectral cues. Listeners identify the location of the loudspeaker emitting the sound, and testing is done in quiet, and with background noise at SNRs that vary from negative to positive values. Data are analyzed to yield root mean square error for localization, patterns of localization within a hemifield and across a hemifield, as is standard in the Litovsky lab (Litovsky et al., 2006; 2009).

## **2.2 Secondary Objective(s)**

- SSD patients with significant tinnitus will be identified using the Tinnitus Handicap Inventory (THI) questionnaire, which is a validated measure of the degree to which tinnitus can adversely affect patients. The THI administered preoperatively and at 3, 6 and 12 month intervals following CI surgery will provide a primary measure of tinnitus relief. A secondary measure, obtained at the same time points, will be tinnitus loudness (1) rated by the patient on a 0 – 10 scale and (2) measured as the level of sound stimulation of the hearing ear needed to match the loudness of the sound to that of the tinnitus. Auditory brainstem responses (ABR) to monaural sound stimulation of the hearing ear (specifically wave V amplitude) will be measured pre- and 6 months post-operatively to test whether CI use reverses previously-documented brainstem hyperactivity related to tinnitus (Gu et al., 2012; Schaette and McAlpine, 2011).

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### 3. STUDY DESIGN

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#### 3.1 Study Design Description

The study of the MAESTRO Cochlear Implant system in patients with single sided deafness will be conducted as a prospective study with ten patients undergoing cochlear implantation (ten patients total). Pre-operative baseline measures will be obtained as outlined below. Post-operative evaluations will be conducted at initial device activation, and three, six, and twelve months post-activation. Because the presence or absence of a cochlear implant 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.

Candidates that are suitable for surgery will undergo placement of a cochlear implant. The cochlear implant wires will then be placed in the cochlea 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 overlying subcutaneous tissue and skin will then be closed and covered with dressings using standard surgical techniques. Intra-operative imaging with a reverse Stenver X-ray will be performed to confirm proper electrode placement.

Following surgical implantation of the MAESTRO Cochlear Implant and two to three weeks of healing, the device will be activated and auditory performance will be assessed at the time of activation and at three, six, and twelve months post-activation. Subjects will be evaluated with the prior approved cochlear implant speech processor programmed with an approved sound-processing algorithm. Post-operative auditory function will be tested with a battery of pure tone threshold audiometry, word recognition testing, and spatial hearing testing. The degree of tinnitus present will be assessed using the Tinnitus Handicap Inventory.

The detailed list of assessments includes:

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#### Prior to Surgery

Important baseline and control tests will be performed pre-operatively to obtain data for comparison. These will include:

- Modified Hearing Handicap Inventory and Quality of Life (SF-36) questionnaires will be administered (see attached)
- Tinnitus Handicap Index and Auditory Brainstem Response (ABR) testing
- Psychophysical measures
- Spatial hearing testing at the Binaural Hearing and Speech Lab at the University of Wisconsin – Madison (Dr. Ruth Litovsky's lab)

#### Initial Activation

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

- Modified Hearing Handicap Inventory and Quality of Life (SF-36) questionnaires will be administered (see attached)
- Detection measures
- Psychophysical measures
- Safety measures

#### Three, Six, and Twelve Months Post-activation Visits (to MEED):

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

- Modified Hearing Handicap Inventory and Quality of Life (SF-36) questionnaires will be administered (see attached)
- Pure tone threshold audiometry at each post-activation interval
- Word recognition testing at each post-activation interval
- Tinnitus assessment at each post-activation interval, along with ABR testing at the six month mark
- Psychophysical measures at each post-activation interval
- Safety measures at each post-activation interval

Visit to University of Wisconsin – Madison after Twelve Months Post-activation:

Once time has been established to acclimate to the cochlear implant, subjects will undergo study-related spatial hearing testing in addition to clinical follow up visits. Depending on subject availability in schedule, the following procedure will take place unless otherwise specified:

- Spatial hearing testing at the Binaural Hearing and Speech Lab at UW – Madison (Dr. Ruth Litovsky's lab)

### **3.2 Allocation to Treatment**

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

#### **3.2.1 Randomization Procedures: N/A**

#### **3.2.2 Masking Procedures: N/A**

- **3.2.3 Breaking the Mask: N/A**

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## **4. SUBJECT SELECTION**

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### **4.1 Subject Inclusion Criteria**

- 18 years of age or older with the ability to provide informed consent
- English as the primary language
- Medically and psychologically suitable
- Willing to receive/have received meningitis vaccinations
- Unsuccessful trial of non-invasive hearing amplification devices or tinnitus treatment as defined by standard of care of six months
- Able to pay for all care received through the study, either through the subject's insurance company or through self-pay
- Able to comply with study requirements, including travel to the investigational sites
- Severe to profound sensorineural hearing loss ( $\geq 70$  dB thresholds between 500 and 4000 Hz) in the worse ear with  $\leq 20\%$  CNC word scores
- Duration of single-sided deafness  $\geq$  one year
- Tinnitus localized to the affected ear, both ears or in the head localized to the affected ear, both ears, or in the head
  - Expected subjects include those with:
    - Unilateral hearing loss secondary to viral or bacterial infection, such as meningitis or labyrinthitis
    - Ménière's disease
    - Sudden sensorineural hearing loss
    - Vascular disease affecting the inner ear
    - A combination of any number of the above conditions

### **4.2 Subject Exclusion Criteria**

- Duration of single-sided deafness  $\geq$  ten years
- Pure tone thresholds  $\geq 35$ dB at 500, 1000, 2000, and 4000 Hz in the better ear
- CNC word scores  $\leq 70\%$  in the better ear

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- Chronic otitis media in either ear
- Inner ear malformation in either ear
- Autoimmune inner ear disease (fluctuation sensorineural hearing loss in either ear)
- Evidence of retrocochlear pathology, including vestibular schwannoma
- Unilateral tinnitus in the unaffected ear
- Cochlear ossification
- Demonstrated cognitive and/or developmental challenges
- Major depression or anxiety; post-traumatic stress disorder; substance abuse
- 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: We will specifically ask all women of childbearing age if there is a possibility they are pregnant or trying to become pregnant at the initial clinic visit; any women who are pregnant or actively trying to become pregnant will be excluded. In cases that are questionable on the day of planned surgery, a pregnancy test will be performed as per current MEEI anesthesia pre-operative protocols.

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

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### **5.1 Study Drug/Device Information**

The MAESTRO Cochlear Implant system consists of a receiver/stimulator, a pocket sized speech processor worn on the body, and a microphone/headset. The system consists of an internal receiver/stimulator and an external audio processor. During surgery, a receiver/stimulator is implanted behind the ear. A wire leads from the receiver/stimulator to the nerve fibers of the cochlea. The audio processor picks up sound and transduces 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 cochlea. This signal is transmitted through the auditory nerve to the brain.

The MAESTRO Cochlear Implant system is marketed under the brand name of MAESTRO Cochlear Implant and manufactured by MED-EL Corporation, USA (Durham, NC). The FDA has approved use of this cochlear implant device in patients with bilateral deafness.

### **5.2 Study Drug/Device Compliance/Adherence**

Because the cochlear implant system is an implanted device, there are few concerns regarding compliance and adherence compared to most drug-based clinical trials. Our study is designed as a prospective, repeated-measure single subject trial. Participants in the experimental group will serve as their own controls. 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 cochlear implant 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 cochlear implant system, if a given subject is non-compliant or non-adherent with use of the cochlear implant 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 one year after cochlear implant surgery. Any patient choosing to withdraw from the study will be replaced by a new study participant recruited from the clinic. The reasons for withdrawal or termination will of course be reported and documented at the time of occurrence.

If a subject withdraws or is terminated after implantation, a new subject will replace him or her. In principle, then, more than 10 subjects may end up with an implant based on their participation in the study.

### **5.3 Study Drug Supplies**

The MAESTRO Cochlear Implant system is already FDA-approved for use in patients with bilateral deafness. As with other cochlear implants, the MAESTRO Cochlear Implant device is ordered prior to surgery. As the MAESTRO Cochlear Implant System is already being used in patients with bilateral deafness, standard storage, dispensation, handling, and disposal protocols are already in place. Similar protocols will be used in our study. In particular, upon receipt the device will be kept in storage with other electrical implant devices at MEEL, and at the time of surgery, dispensed/opened and subsequently handled with appropriate sterile technique.

### **5.4 Study Drug/Device Storage and Accountability**

The cochlear implant system is stored at room temperature upon receipt and kept securely until it is used during surgery. Cochlear implants utilized for this study will be kept separate from devices for clinical use within device locked storage. Given its electronic components, prolonged exposure to extreme temperatures should be avoided. In our study, the cochlear implant system will be kept in storage with other electrical implant devices at MEEL, 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 MAESTRO cochlear implant 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**

Our study does not include the planned use of other medications concomitantly with the MAESTRO Cochlear Implant. If patients experience complications or medical concerns related to the cochlear implant device, 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.

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**6. BIOSPECIMEN COLLECTION (IF APPLICABLE)**

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Biospecimens will not be collected as part of our study. Thus, specimen preparation, handling and storage 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

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## **7. STUDY PROCEDURES**

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### **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 a physical exam will be completed. Subjects will also be evaluated for baseline qualitative measures using questionnaires and quantitative measures using audiologic testing.

In accordance with 21 CFR 812.25 (c), we will attempt to match the proportions of women and minorities included in past trials for the indication of CI surgery in patients with SSD. We will also attempt to include an even distribution of patients with regards to age, sex, race and ethnicity as there is no particular population of patients affected by the conditions addressed by our study. However, given the small sample size of our study, it will be difficult to capture all patient demographics.

### **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, Abbreviated Profile of Hearing Aid Benefit (APHAB), the Speech Spatial and Qualities of Hearing Scale (SSQ) and Quality of Life (SF-36) questionnaires as well as audiologic tests such as Early Speech Perception Testing and Consonant-Nucleus-Consonant testing. The degree to which tinnitus in the non-hearing ear affects the participant's well-being will be assessed using the Tinnitus Handicap Inventory. Auditory Brainstem Response (ABR) will be measured in patients with tinnitus as an additional clinical correlation, conducted for research purposes. Finally, patients will travel to the Binaural Hearing and Speech Lab at the University of Wisconsin – Madison for hearing-in-noise and spatial hearing testing pre- and post-operatively (see below). All costs for airfare, accommodations, meals and a daily stipend will be covered by funding from Dr. Litovsky's laboratory.

### **7.3 Study Drug or Device Procedures**

Subjects will undergo pre-operative evaluation for cochlear implant surgery. Those subjects that are appropriate for surgery will undergo a procedure for implantation of the MAESTRO Cochlear Implant system. As per manufacturer protocol, the parameters of the cochlear implant system 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 cochlear implant device.

### **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**

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 weeks, and at three, six, and twelve months. 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 cochlear implant 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 attached.

## **8. SAFETY AND EFFECTIVENESS ASSESSMENTS**

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### **8.1 Safety Assessments**

Safety assessments will include questionnaires to assess for complications 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 MED-EL Corporation (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:

- Pure Tone Threshold Audiometry
- Sound Localization Testing (University of Wisconsin - Madison)
- Speech Perception Measures - Consonant-Nucleus-Consonant (CNC) Testing
- Psychophysical Measures
- Tinnitus Assessment - Tinnitus Handicap Inventory (THI)
- Subjective Questionnaires - Hearing Handicap Inventory, Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire, Speech Spatial and Qualities of Hearing Scale (SSQ), and Quality of Life (SF-36) questionnaire

Each CI subject's speech perception ability will be ranked on a continuum of performance by using standardized speech perception tests that document the range of perception abilities. We will use the Consonant-Nucleus-Consonant (CNC) test (House Ear Institute). The CNC open set single-syllable test will be administered and scored both for whole-word and phonemic items. All speech tests will use recorded materials at a level of 65dB HL and will be presented in the soundfield through a speaker to the subject at 0 degree azimuth and calibrated at a set

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distance, typically 1 meter. We will test SSD patients in the bilateral condition, using the good ear only and use contralateral masking to eliminate contributions from the good ear to evaluate the implanted ear.

Each subject's spatial hearing ability will be assessed in collaboration with Dr. Ruth Litovsky at the University of Wisconsin. Subjects will identify a single word randomly chosen from a set of fifty possibly alternatives and presented from a loudspeaker directly in front of the subjects. Speech intelligibility will be tested by masking sentences co-presented at different spatial configurations. The presentation level of the target speech will be varied in order to generate different signal-to-noise ratios at each condition. We will evaluate implanted SSD patients with the device turned on and off to directly evaluate contribution of the cochlear implant to understanding speech-in-noise.

Recorded test materials, test keys and patient response forms will be collected and documented as part of the study. Number of test items and percentage scores on each test will be documented and included in the data analysis.

- All subjective questionnaires will serve as an additional qualitative assessment of hearing and will not be used to directly guide quantitative audiologic testing. Measures from subjective questionnaires will be carefully documented for each subject and included in data analysis. These questionnaires will be completed before the activation appointment and prior to each of the follow-up appointments.

## **9. ADVERSE EVENT RECORDING AND REPORTING**

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### **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 cochlear implant system.

Adverse events or abnormal test findings felt to be associated with the cochlear implant 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

➤ **CASUALTY AND SEVERITY ASSESMENT**



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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 MAESTRO cochlear implant system; 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 cochlear implant system 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 EVENTS TO FDA**

- Written IDE Safety Reports
- Telephoned IDE 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 MED-EL Corporation, which has provided a Right of Reference Letter for the MAESTRO Cochlear Implant system in accordance with their respective reporting guidelines.

### **➤ Reporting Adverse Events to the Human Studies Committee**

- The Principal Investigator will reports to the HSC any serious adverse events that are unexpected and related/possibly related to research within 7 calendar days from the time the PI became aware of the event.
- Any unexpected and study-related death will be reported to the HSC within 24 hours of PI's knowledge of the event by email or telephone.
- The PI will report to the HSC all non-serious adverse events that are unexpected and related or possibly related to the research within 30 calendar days from the time the PI became aware of the event.

- The PI will promptly report to the HSC Unanticipated Problems (UAPs) involving risks to the subjects or others.

### **9.3 Withdrawal of Subjects due to Adverse Events**

#### **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**

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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

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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 withdraws from the study due to an adverse event, he/she will be replaced by recruiting a new study participant from clinic. The reasons for withdrawal or termination will of course be reported and documented at the time of the occurrence. In principle, then, more than 10 subjects may end up with an implant based on their participation in the study.

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## 10. STATISTICAL METHODS/DATA ANALYSIS

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

The study has a primary endpoint of one year following cochlear implant surgery for ten 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, audiologic tests, questionnaires on efficacy, and safety measures as a comprehensive method for assessing the outcomes of cochlear implant surgery. In particular, the use of these measures will allow us to obtain both objective and subjective data to assess the safety and efficacy of cochlear implant placement in patients with single sided deafness and thereby understand how cochlear implant placement has influenced patients' hearing and quality of life. By comparing our findings and measures to data obtained in other patient populations (such as patients with single sided deafness who do not undergo cochlear implantation), we will better understand whether cochlear implant placement in this patient population has improved safety and efficacy compared to no treatment.

### 10.2 Secondary endpoints or outcome measure(s)

The secondary outcome measure of this study is the effect of cochlear implantation on tinnitus suppression in patients with tinnitus in the non-hearing ear. Outcomes will be assessed using the Tinnitus Handicap Inventory and auditory brainstem response testing as previously indicated. Prior studies have indicated that cochlear stimulation via a cochlear implant device can suppress tinnitus. By comparing our findings and measures to data obtained from patients with single sided deafness who do not undergo cochlear implantation, we will better understand the utility of cochlear implantation for tinnitus suppression in this patient population.

### 10.3 Sample Size Determination

Our study will recruit ten participants for placement of a MAESTRO Cochlear Implant device with follow-up measurements and assessments for one year post-operatively. Although our study is limited to a small sample size of ten 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 cochlear implants in patients with single sided deafness. Given that single-sided deafness is an experimental indication for cochlear implantation, it is appropriate to assess efficacy in a small cohort prior to recruiting more subjects. This will allow us to avoid unnecessary surgery in patients who may not benefit from this intervention.

#### **10.4 Analysis Population**

Given the small sample size of ten patients 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**

As this study is a single-subject research design, cochlear implant 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. Audiometric and psychoacoustic performance data from the same ear in a subject will be evaluated both prior to and following cochlear implant placement. 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**

Cochlear implant 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 patients enrolled in the current study will be compared to data collected from patients with single sided deafness who do not undergo cochlear implantation 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 Analyses**

- Interim analyses will be completed once three, five, and eight patients are enrolled. These analyses will be completed at six months and one year post-operatively for each of these cohorts. Study staff and the Investigator will perform the interim analyses, 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.

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## **11. DATA AND SAFETY MONITORING**

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### **11.1 Data and Safety Monitoring Plan**

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 cochlear implant 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. Study activity will be reviewed monthly by the MEEI implant board and annual reports will be submitted to both the FDA and the HSC to ensure compliance with the approved protocol.

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. As there will be data collected at both MEEI and the University of Wisconsin, data will be analyzed both on-site at MEEI and in a centralized, secure database that allows for sharing of results between the institutions. The staff at the University of Wisconsin that will be conducting the auditory testing will have access to the approved case reporting forms for the recording of all test results. These results will be shared through the secure MEEI storage website. If any urgent issues arise at either site, the primary site investigators will be notified immediately by telephone or secure e-mail. The teams at both sites will be thoroughly informed of the timeline for reporting adverse events or issues to the HSC and FDA. This information will be communicated securely both in paper form and via secure e-mail. Any significant non-compliance with this protocol will be addressed immediately by the Principal Investigator and the issues will be reported to the



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HSC. If the Investigator is unable to successfully address the issue, any non-compliant study staff will be removed from the study protocol and denied access to the secure patient information.

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. This individual will receive the required online training required for handling protected patient information and will have an in-depth understanding of the protocol such that he or she is able to identify issues with data or safety in a timely manner.

A monitoring log will be kept securely within MEEI or the office of the research assistant. The log will abide by the guidelines set forth by the FDA and HSC, and will consistently be updated with the most recent data.

- We do not feel that a Data and Safety Monitoring Board is required for this study as the cochlear implant device has already been approved for use in adults with bilateral hearing loss and therefore the risks are well known.

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## **12. DATA HANDLING, RECORD-KEEPING AND MONITORING**

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### **12.1 Data Recording, Record-Keeping, and Monitoring**

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 MEEI. Electronic systems used are in compliance with FDA electronic records and signature regulations. Data review will be the responsibility of the PI and other members of the study staff.

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## **13. STUDY DISCONTINUATION CRITERIA**

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### **13.1 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 agree to measurements of clinical outcomes and assessments of device safety, their data will be collected until one year following cochlear implantation surgery. As with other criteria for withdrawal, subjects that are withdrawn will be replaced through recruitment of additional study participants in clinic.

### **13.2 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

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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 cochlear implantation 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.

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## **14. APPENDICES**

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### **14.1 Schedule of Events**

**14.2 Case Report Forms: see multiple attached documents, each labeled “CRF”**

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**Schedule of Events**

(M = Billable to Medicare/Insurance/Third Party)

List of Procedures	Billable to:	Pre-Operative			Day of Surgery	Post-Operative Visits					
		Visit 1	Visit 2	Visit 3	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		SCREENING	PRE-OP	SOUND LOCALIZATION	DAY 0	DAY 7, +/- 7 DAYS	WEEK 4, +/- 2 WKS	3MOS, +/- 4 WKS	6MOS, +/- 4 WKS	12MOS, +/- 4 WKS	Sound localization
<b>SIGN INFORMED CONSENT</b>	N/A	X									
<b>EXAMINATION</b>	M	X									
<b>QUESTIONNAIRES</b>	N/A		X					X	X	X	
<b>PRE-OPERATIVE VISIT</b>	M		X								
<b>AUDIOLOGIC TESTING</b>	M	X									
<b>Tinnitus Handicap Index</b>	N/A		X					X	X	X	
<b>Auditory Brainstem Response</b>			X						X		
<b>CNC Test</b>	M	X					X	X	X	X	
<b>COCHLEAR IMPLANTATION</b>	M				X						
<b>POST-OP VISIT</b>	M					X	X				
<b>CI ACTIVATION</b>	M						X				
<b>SAFETY MEASURES</b>	N/A						X	X	X	X	
<b>*Sound Localization Testing</b>	N/A			X						X	X

\*Sound localization testing to be performed at the Binaural Speech and Hearing Laboratory at the University of Wisconsin - Madison