Cochlear Implantation in Adults with Asymmetric Hearing Loss Clinical Trial

Protocol

Version 1.4

NCT03052920

December 5, 2014
Revised January 4, 2015
Revised January 12, 2017
Revised June 1, 2017
Revised April 27, 2018

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Introduction

The advantages of binaural hearing (listening with two ears) over monaural hearing (listening with one ear) have been well documented and include sound localization, speech understanding in noise, judgments of distance and movement, and detection of soft or distant speech (Cochran et al., 1968; Durlach and Colburn, 1978; Grantham, 1986; Bronkhorst and Plomp, 1988, 1989; Akeroyd, 2006; Colburn et al., 2006). These advantages are achieved by the ability to receive and compare acoustic signals from two ears. Because ears are spatially separated, the sound received at each ear differs in both time and amplitude information. For example, whether localizing a sound or listening in noise, one ear is typically closer to the signal than the other, with the head acting as a barrier between the ears. Consequently, the signal arrives at the near ear before the far ear, creating discrepancies in arrival time referred to as interaural time differences (ITDs). Furthermore, because the head impedes the sound, the signal has greater amplitude at the near ear compared to the far ear, which results in loudness differences between the ears referred to as interaural level differences (ILDs). All audible sounds generate both ITDs and ILDs that are crucial for central processing of auditory information. The ability to reconcile these differences with great precision enables binaural listeners to localize sound and understand speech in background noise with little effort. Having input to both ears also provides a redundant signal to the auditory system, which is important for understanding soft speech and hearing distant sounds (Levitt and Rabiner, 1967a, b; Morera et al., 2005; Morera et al., 2012). Studies utilizing self-assessment questionnaires have confirmed that monaural listeners perceive deficits in everyday communication for understanding soft speech and speech in noise as well as for spatial hearing. Moreover, studies have identified secondary effects of hearing loss such as fatigue, increased effort, anxiety and social isolation (Hétu et al., 1988; Ringdahl and Grimby, 2000; Hicks and Tharpe, 2002; McCoy et al., 2005; Nachtegaal et al., 2009). The degradation or complete loss of binaural abilities can have a significant impact on daily communication and overall quality of life.

Individuals with asymmetric hearing, that is, one ear with moderate hearing loss and one ear with severe to profound hearing loss (SPHL), lack binaural input and are thus unable to attain binaural hearing advantages. Clinically, attempts to fit amplification in the poor ear with SPHL are problematic due to the severity of the hearing loss and the limitations of hearing aid (HA) technology, which result in insufficient gain and reduced sound quality. Patients often discontinue amplification in this ear due to lack of perceived benefit and are consequently rendered monaural listeners (Kochkin, 2010; Kaplan-Neeman et al., 2012). Interestingly, Noble and Gatehouse (2004) reported that patients with asymmetric hearing were significantly more disabled than those with symmetric hearing loss for speech recognition, spatial hearing and quality of sound.

A treatment option for individuals with asymmetric hearing loss is a bilateral contralateral routing of the signal HA (BiCROS) (Oeding and Valente, 2013). This system consists of a transmitter worn on the poor ear that picks up sound through a microphone and a HA with an integrated receiver that is worn on the better ear. The HA provides amplification

to that ear and also receives the sound from the microphone worn on the poor ear. In other words, sound from the poor side is routed via wireless transmission to the better hearing ear. Although a BiCROS HA allows sound to be detected from both sides of the head, all sound is heard by the better ear. New technology, such as improved digital signal processing and noise reduction circuitry, has been implemented in current BiCROS HAs in hopes of improving performance; these features were preferred by individuals who used older BiCROS technology (Williams et al., 2012; Oeding and Valente, 2013). However, test measures, specifically testing in noise, did not show a significant difference in performance between newer and older BiCROS technology. In fact, Oeding and Valente (2013) found no difference between the unaided test condition and three BiCROS test conditions (no noise reduction circuitry, mild noise reduction, and maximum noise reduction). Williams et al. (2012) also reported no statistically significant improvement when testing in noise with newer versus older BiCROS technology. Furthermore, group mean scores in noise were no different when participants were tested with just a HA on the better ear (nothing on poor ear) versus the full BiCROS system. These results were consistent regardless of the technology used (i.e., new or older). A significant limitation of the BiCROS HA is that it does not provide binaural input. As a result, individuals fit with a BiCROS are unable to take advantage of ITDs and ILDs, which are necessary for binaural processing to improve speech understanding in noise. As noted above, ITDs and ILDs are also necessary for sound localization. The research in this area (BiCROS and sound localization) is sparse; however, Arndt et al. (2011) evaluated localization abilities of 11 individuals who had worn a contralateral routing of the signal (CROS) device for three weeks. These individuals had one ear with SPHL and one ear with normal hearing. Like the BiCROS system, the CROS device routes the signal from the poor hearing side to the good hearing side but does not provide amplification to the better (normal hearing) ear. Results of the Arndt study revealed no difference in sound localization ability between the CROS device and no device conditions. Therefore, it is unlikely that a BiCROS HA would be beneficial in localizing sound. Again, because the BiCROS and CROS systems do not restore hearing to the poor ear, individuals using this technology do not receive binaural cues, such as ILDs or ITDs and consequently, cannot achieve advantages derived from binaural hearing.

The treatment option most typically used for individuals with asymmetric hearing loss is a HA fitted to the better ear only and no HA in the poorer ear. As stated above, fitting a HA to an ear with a SPHL and poor word recognition is generally unsuccessful and therefore not routinely done for individuals with a better hearing ear. Insufficient gain, poor sound quality, and lack of perceived benefit when the poor ear is aided are common concerns. Additionally, it is often assumed that these individuals can function sufficiently well with conventional amplification in the better ear alone. A weakness of this assumption is that fitting of amplification in one ear does not allow ITD or ILD comparisons and all binaural processes are lost. Therefore, optimized auditory function for real-life listening in conditions of noise, reverberation, speaker variation and distance is virtually eliminated.

Adult cochlear implant (CI) candidates typically have moderate to profound or severe to profound hearing loss in both ears. In these cases, one ear or both ears may be implanted. In cases of bilateral implantation, many studies have shown the feasibility of integrating signals from both ears, providing bilateral CI recipients the highly beneficial effects of bilateral input including better speech understanding in quiet and in noise, better understanding of soft speech and improved localization compared to a unilateral

CI (Litovsky et al., 2006; Buss et al., 2008; Dunn et al., 2012; Reeder et al., 2014). A number of studies have also examined effects of bimodal input, listening with a CI in one ear and a HA in the other, in comparison to a unilateral CI alone (Tyler et al., 2002; Morera et al., 2005; Ching et al., 2007; Potts et al., 2009; Morera et al., 2012). Participants in these studies had very little residual hearing in the non-implanted ear; the majority had moderately-severe-to-profound or severe-to-profound hearing loss in the non-implanted ear. Even so, the results revealed improved speech understanding in noise, improved speech understanding in quiet at both conversational and soft listening levels, and improved localization abilities in the bimodal listening condition (CI + HA) compared to the CI alone listening condition. In addition, participants preferred the combined input from a CI in one ear and a HA in the other, and showed higher ratings compared to either the CI or HA alone conditions on self-assessment questionnaires that probe communication functioning in everyday situations (Potts et al., 2009; Dwyer et al., 2014).

Recent studies at Washington University School of Medicine in St. Louis have investigated the effects of asymmetric hearing loss and the possibility of restoring binaural abilities through cochlear implantation. Study participants had at least a moderate-to-profound hearing loss in one ear (that received a CI) but less hearing loss in the opposite ear (that continued HA use). Initial results from 10 participants indicated the CI successfully restored hearing to the poor ear by improving hearing detection in the sound field. In general, CI sound field threshold levels from 250-6000 Hz were 30 dB HL or better (Firszt et al., 2012). Adults with postlingual hearing loss demonstrated significant open-set speech recognition in the implanted ear at the six month test interval for measures in quiet and noise (Firszt et al., 2011; Firszt et al., 2012). In addition to improved audibility and speech recognition with the implant in the poor hearing ear, study participants demonstrated significantly improved speech recognition and localization when comparing the six-month bimodal condition (CI + HA) to the pre-implant, everyday listening condition (HA in the better ear alone) (Firszt et al., 2012). For sentences presented at a soft level in quiet and for localization, scores at the six-month test interval were significantly better in the bimodal condition than the HA in the better ear alone condition. Furthermore, the improvements seen between pre- and post-implant test conditions were supported by participant reports on the Speech, Spatial and Qualities of Hearing Scale (SSQ), (Firszt et al., 2012; Dwyer et al., 2014).

In summary, many hearing-impaired patients function with noticeable hearing asymmetry. When hearing is asymmetric and the loss in the poor ear is moderate-to-profound, lack of treatment for that ear is very common, which results in monaural hearing. Listening with just one ear, particularly a hearing-impaired ear, is detrimental to signal segregation and communication. Individuals with asymmetric hearing loss frequently seek medical care due to pervasive communication difficulties. The only available treatment that can provide hearing to the deaf ear is a CI. At this time, individuals with asymmetric hearing loss are not routinely implanted in the poor hearing ear simply because the contralateral, better hearing ear has hearing loss in the moderate range rather than the severe to profound range. A prospective, single-arm, multi-center clinical trial is critically needed to address the deficits of patients with asymmetric hearing loss and explore potential treatment with a CI. Outcomes from this study will also inform a future pivotal clinical trial.

Study Objectives

Primary Objective: Obtain preliminary efficacy data in adults with asymmetric hearing loss who receive a cochlear implant (CI) in the poor hearing ear and maintain a hearing aid (HA) in the better hearing ear. Efficacy is defined as post-implant improvement in the poor ear with a CI compared to pre-implant with a HA. Measures are sound field threshold levels and CNC monosyllabic words in quiet.

Secondary Objectives:

1. Obtain efficacy data related to bimodal hearing. Efficacy is defined as post-implant improvement (CI in poor ear + HA in better ear) compared to the pre-implant best-aided condition (either HAs in both ears, or a HA in the better ear alone for adults with no aidable hearing in the poor ear). Measures are sound localization, speech recognition in noise, speech recognition at soft presentation levels, perceived hearing handicap, and reported quality of life.
2. Evaluate safety associated with cochlear implantation in individuals with asymmetric hearing loss. The safety evaluation will be based on the number, type and degree of all adverse events.
3. Collect essential preliminary information related to test measures and methodology that can be used clinically in a future Phase III clinical trial (e.g., localization, listening in noise, listening at soft levels).

Study Design

The study will be conducted as a multicenter, prospective, single-arm clinical trial, evaluating the efficacy and safety of cochlear implantation in patients with asymmetric hearing loss. A repeated-measures analysis will be employed whereby patients will act as their own controls. Thirty-seven individuals with asymmetric hearing loss will participate at three to four investigational sites. Participants will be recruited from surgeons and audiologists in Otolaryngology departments at the participating sites. Prior to receiving a CI in the poor hearing ear, participants will be evaluated as follows:

- HA in the better ear alone
- HA in the poor ear alone
- Bilateral HAs

Post-implant evaluations will occur at 3, 6, 9, and 12 months after initial stimulation of the CI. Participants will be evaluated as follows:

- HA in the better ear alone
- CI in the poor ear alone
- HA and CI together

The study length for individual participants will be approximately 18 months. The overall study is expected to last approximately 5 years.

These study results are essential for the development of a Phase III multi-center clinical trial, helping to refine inclusion/exclusion criteria, test protocols, pre-implant baseline condition(s), and final sample size estimates.

Device Descriptions

Participants will be counseled and provided information regarding the CI devices commercially available in the United States. Currently, there are three devices, each manufactured by a different company: Advanced Bionics, LLC, Cochlear Americas, and Med-EL Corporation. In consultation with the participant's audiologist and surgeon, the participant will chose the device that best fits the participant's lifestyle and preferences (e.g. ease of controls, size, water resistance, warranty length, available accessories, or other speech processor features). The CI surgeon will have the final recommendation if there is a surgical preference. We plan to recruit at least 10 participants with each of the three devices.

Advanced Bionics LLC

The HiResolution™ Bionic Ear Cochlear Implant System consists of 1) the implanted device, the HiRes90K™ Advantage Cochlear Implant with HiFocus™ Mid-Scala electrode; 2) the externally worn Naida behind-the-ear speech processor and/or Neptune body-worn speech processor; and 3) the SoundWave 2 custom fitting software used to program the speech processors. Subject to change as commercial availability changes.

Cochlear Americas

The Cochlear™ Nucleus™ Cochlear Implant System consists of 1) the implanted device, CI24 RE (Contour Advance), and the CI422 (Slim Straight); 2) the externally worn Nucleus 6 speech processor; and 3) the Custom Sound fitting software used to program speech processors. Subject to change as commercial availability changes.

Med-EL Corporation

The Med-EL Maestro™ Cochlear Implant System consists of 1) the implanted device, the Concert™ Medium or Standard; 2) the externally worn Opus 2 speech processor and/or Rondo speech processor; and 3) the Maestro System fitting software used to program speech processors. Subject to change as commercial availability changes.

Participant Population

Thirty-seven to forty individuals with asymmetric hearing loss will participate at three to four U.S. CI centers. Participants will be sequentially recruited into the study to ensure a participant pool representative of the general adult population with asymmetric hearing loss. Participants will not be pre-selected based on age (other than being at least 18), gender or ethnicity. Each participant will meet the following inclusion and exclusion criteria:

Inclusion Criteria

- 18 years of age or older
- Proficient in English
- Have a desire for functional binaural hearing
- Have failed a previous HA treatment for asymmetric hearing loss (BiCROS or poor ear HA) or willing to complete a trial if necessary
- Willingness to comply with all study requirements
- Ability to provide informed consent
- Poor ear (ear to be implanted):
    - Pure-tone average (PTA) at .5, 1 and 2 kHz > 70 dB HL (hereafter referred to as severe to profound hearing loss – SPHL)
    - Aided word recognition score (CNC Word Test) at 60 dB SPL ≤ 30%

    - Duration of SPHL ≥ 6 months
    - Onset of hearing loss ≥ 6 years of age
- Better ear:
    - PTA at .5, 1, 2, 4 kHz of 40 to 70 dB HL
    - Currently using a HA
    - Aided word recognition score (CNC Word Test) at 60 dB SPL > 40%
    - Stable hearing for the previous 1-year period. "Stable" is defined as thresholds that have not changed by more than 10 dB at 2 or more octave interval audiometric frequencies

Exclusion Criteria

- Medical condition that contraindicates surgery
- Actively using an implantable device in the ear to be implanted
- Known cochlear malformation or obstruction that would preclude full insertion of the electrode array in the ear to be implanted
- Hearing loss of neural or central origin
- Unrealistic expectations related to the benefits and limitations of cochlear implantation
- Unwillingness or inability to comply with all investigational requirements

Spouse/Significant Other

The spouse/significant other of the cochlear implant study participants will also be asked to participate in the study. They will be asked to complete questionnaires that examine the impact of asymmetric hearing loss and cochlear implantation on communication function, personal adjustment, and social-emotional aspects of daily life. The information collected will relate to both the cochlear implant study participant as well as the spouse/significant other.

Investigation Procedures

Test Measures

All testing will take place in a sound booth using calibrated equipment and test stimuli.

Unaided Audiometric Threshold Levels

Air and bone conduction audiometric threshold levels in dB HL will be obtained for both ears using standard audiometric test procedures (Carhart and Jerger, 1959).

Air conduction threshold levels, using insert earphones, will be obtained at 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz. When necessary, narrow band noise will be used to mask the better hearing ear.

Bone conduction threshold levels will be obtained at 250, 500, 1000, 2000, 3000 and 4000 Hz. When necessary, narrow band noise will be used to mask the better hearing ear.

Aided FM, Tone Sound Field Threshold Levels

Sound field threshold levels will be obtained in the sound booth using frequency modulated (FM) tones presented through a loudspeaker situated at ear level at 0° azimuth. The loudspeaker will be located 1.5 meters from the center of the participant's head. Sound field levels will be obtained in dB HL at 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz. Levels will be obtained at each frequency in 2 dB steps using the

Hughson-Westlake procedure (Carhart and Jerger, 1959). Participants will be instructed to press the response button every time the tone is heard, even if the tone is very soft.

Consonant-Vowel Nucleus-Consonant (CNC) Word Test

The CNC monosyllabic word test (Peterson and Lehiste, 1962) is part of the Minimum Speech Test Battery (Luxford and Ad Hoc Subcommittee, 2001) for CI candidates and recipients. The test consists of 10 lists of monosyllabic words with 50 words per list. The words are spoken by a male talker; each word is preceded by the carrier "ready."

CNC word testing will be administered in the sound field through a loudspeaker at ear level at 0° azimuth and 1.5 meters from the center of the participant's head. The test will be presented at 60 dB SPL. Participants will be instructed to repeat the word that is heard and will be encouraged to guess when possible. The tester will write down the participant's response and words will be scored as a percent correct.

AzBio Sentence Test

The AzBio Sentence Test (Spahr et al., 2012) consists of 33 lists of 20 sentences per list and is part of the 2011 New Minimum Speech Test Battery for Adult Cochlear Implant Users. AzBio sentences are spoken by four talkers, two males and two females; each talker presents five of the 20 sentences. The sentences are spoken in a conversational style, are 4-10 words in length, and approximate a fourth grade reading level (King et al., 2012).

The sentences will be presented in the sound field through a loudspeaker (0° azimuth, 1.5 meters from center of participant's head) at 60 dB SPL, at 50 dB SPL and at 60 dB SPL in 4-talker babble noise using a +8 dB signal-to-noise ratio (SNR). When sentences are presented in 4-talker babble noise, sentences and noise will be presented through the same loudspeaker (0° azimuth). The participant will repeat as much of the sentence as possible. The test will be scored as percent correct.

Bamford-Kowal-Bench Speech-in-Noise (BKB-SIN) Test

The BKB-SIN Test (Etymotic Research, 2005) will be administered in the sound field at 65 dB SPL with sentences presented from the front loudspeaker (0° azimuth) and 4-talker babble noise presented from a loudspeaker 90° to the participant's right and 90° to the participant's left. The BKB-SIN Test includes 18 lists of sentences. The sentences are spoken by a single male talker, are 5-6 words in length and are at a 1st grade reading level. The 4-talker babble begins at a +21 dB SNR for the first sentence and decreases by 3 dB after each sentence in order to obtain an SNR-50 score; that is, an SNR for which 50% of the key words are repeated by the participant. The BKB-SIN Test is part of the New Minimum Speech Test Battery for Adult Cochlear Implant Users, 2011.

Localization Test

A localization test will be administered in the sound field with stimuli presented from a 140°, eight loudspeaker array. Loudspeakers will be spaced 20° apart. The participant will sit facing the center of the array (0° azimuth). The loudspeakers are approximately at head level and numbered 1 through 8. The stimuli consist of CNC words presented at 65 dB SPL with the level roved by ± 6 dB. Each CNC word is preceded by the carrier "ready," and both are presented from the same loudspeaker. Prior to the onset of each trial, participants are instructed to keep their gaze fixed at 0° azimuth until the word "ready" is heard, at which point they are free to turn their head if desired. After stating the loudspeaker number from which they heard the word, participants will reposition their gaze to 0° azimuth. Eight words are presented from each of the eight loudspeakers (total of 64 presentations); loudspeaker order is pseudo randomized. A root mean

square (RMS) error score is calculated as the mean source-response difference, irrespective of error direction (the square root of the quotient resulting from the sum of each source-response difference squared and divided by the number of trials). A lower RMS error score indicates less localization error, or greater accuracy. Localization in Noise will be evaluated using the same system and stimuli with the addition of 60 dB SPL restaurant noise originating from all loudspeakers.

Questionnaires

Hearing Handicap Inventory for the Elderly (HHIE)
The HHIE (Ventry and Weinstein, 1982) is a 25-item, self-assessment scale that quantifies the perceived emotional and social/situational consequences of hearing loss. It is composed of 13 emotional subscale items and 12 social/situational subscale items. Each item is a question that the participant answers as "Yes", "Sometimes" or "No". The HHIE can be used to identify changes in handicap scores following a specific treatment or over time.

Health Utilities Index Mark 3 (HUI3)
The HUI3 (Furlong et al., 2001) provides descriptive evidence on multiple dimensions of health status and results in a score for each dimension of health, and a health related quality of life overall score. Health dimensions include vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition. Each dimension has 3- 6 levels of function from which the participant selects the one that best describes their perceived ability. The overall scores are on the conventional scale of dead = 0.00 to perfect health = 1.00. The HUI3 has been used in numerous clinical studies worldwide. The HUI3 can be used to identify current health status as well as a change in health status over time or as the result of a specific event or treatment.

Speech, Spatial and Sound Qualities (SSQ) Questionnaire
The SSQ (Gatehouse and Noble, 2004) is a self-assessment questionnaire. The participant will rate their perceived hearing ability for a number of listening situations. The questionnaire includes a broad range of domains and reflects the individual's perception of functioning in real-world situations. Section I, Speech hearing, probes speech recognition in a variety of sound environments with varying degrees of talker variability. Section II, Spatial hearing, examines three components of spatial hearing, sound direction, distance, and movement. Section III, Qualities of hearing, considers segregation of sound, naturalness, and listening effort.

Glasgow Benefit Inventory (GBI)
The Glasgow Benefit Inventory (Robinson and Summerfield, 1996) was specifically developed for otorhinolaryngological conditions and interventions. The GBI is a post-intervention questionnaire that measures change in health status following surgical intervention, e.g., CI surgery. The GBI was designed to be patient-oriented, maximally sensitive to otorhinolaryngological interventions, and provide a common metric to compare benefit across different interventions. The questionnaire has 18 items and employs a five-point Likert scale that ranges from much better to much worse.

Satisfaction with Amplification in Daily Life (SADL)
The SADL (Uriate et al, 2005) probes patient satisfaction with hearing aids; wording is modified for bimodal listeners. The participant will rate satisfaction for 13 questions that address overall benefit, cost, use, and communication. The participants rate their satisfaction along a 7-point scale from "Not at all" to "Tremendously".

Participant Interview Form

This form guides investigators as they query participants about tinnitus, dizziness, medications, and the incision/implant site (post-implant only). The form will be used pre- and post-implant and will assist investigators in the identification of adverse events.

The Communication Profile for the Hearing Impaired (CPHI) – Communication Performance

The CPHI (Demorest and Erdman, 1987) Communication Performance section is 18 questions focused on situations the participant experiences at home, work and in social situations. The spouse/significant other will complete regarding the participant's communication abilities. Each question is answered along a 5-point scale from "Rarely, Almost Never" to "Usually, Almost Always".

The Hearing Impaired Impact – Significant Other Profile (HII-SOP)

The HII-SOP (Preminger and Meeks, 2010) is designed for the spouse/significant other; and addresses the impact of hearing loss on the spouse/significant other (rather than on the participant). It is comprised of 20 questions that include specific situations related to Communication Strategy, Relationship and Emotions, and Social Impact. The spouse/significant other answers Yes, Sometimes, or No to each question.

Study Schedule

A summary of the pre-implant and post-implant study test visits is provided in the Table on the following page.

Pre-Implant Candidacy Evaluation

The duration of this testing will be approximately 4 hours and will be completed in 1-2 visits.

Informed Consent

A research study team member, either the surgeon or audiologist working with the patient, will identify potential participants. If a patient indicates interest in participation, the surgeon or audiologist will have a detailed conversation about the study procedures, purpose, schedule, and time commitments and provide a copy of the consent document. Potential participants will have the opportunity to take the consent document home to read and discuss with family and friends and will be encouraged to contact the surgeon and/or the audiologist if there are questions. Study team members will ensure that the potential participant is aware of all aspects of cochlear implantation as well as study expectations, the surgical procedure, and the post-implant study schedule. When informed consent is obtained, each section of the consent form will be reviewed and the potential participant will be given an opportunity to ask questions. Individuals who are still interested in participating will sign and date the consent form. Several aspects of the individual's participation will be highlighted during the consent process: (1) participation is voluntary; (2) the participant can withdraw from the study at any point for any reason; and (3) the participant will receive appropriate clinical care whether or not they participate in the study. The participant will be given a copy of the signed consent document.

Summary of Study Schedule

Activity/Measure	Condition	Candidacy Evaluation	Pre-Implant Testing	Initial Stim	Post-Implant 3 mo	Post-Implant 6 mo	Post-Implant 9 mo	Post-Implant 12 mo
Informed Consent		x						
Air Conduction Thresholds	*Each ear alone*	x		x	x	x	x	x
Bone Conduction Thresholds	*Each ear alone*	x						
Sound Field Thresholds	*Each ear alone*	x	x		x	x	x	x
CNC Words @ 60 dB SPL	*Each ear alone*	x			x	x	x	x
	Both ears together		x		x	x	x	x
AzBio Sentences @ 60 dB SPL	*Poor ear alone*		x		x	x	x	x
AzBio Sentences @ 50 dB SPL	*Better ear alone*		x		x	x	x	x
	Both ears together		x		x	x	x	x
AzBio Sentences @ 60 dB SPL +8 dB SNR	*Better ear alone*		x		x	x	x	x
	Both ears together		x		x	x	x	x
BKB-SIN Sentences SF/NR, SF/NL	*Better ear alone*		x		x	x	x	x
	Both ears together		x		x	x	x	x
Localization	*Better ear alone*		x		x	x	x	x
	Both ears together		x		x	x	x	x
HHIE			x			x		
HUI3			x			x		
SSQ			x			x		x
GBI						x		
SADL						x		
Interview Form			x	x	x	x	x	x
CPHI			x			x		
HII-SOP			x			x		

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Hearing History

A complete hearing history will be obtained from the participant. The information obtained from the participant will include etiology of hearing loss, onset of hearing loss, HA use, and duration of SPHL. Previous audiograms to confirm hearing history will be obtained if possible. An area of interest will be previous treatments and results for asymmetric hearing loss, specifically a poor ear HA or BiCROS HA trial. Participants who have never had a failed poor ear HA or BiCROS HA trial will be fit during the Candidacy Evaluation and complete a 1-2 week trial followed by an assessment with the poor ear HA or BiCROS HA (Alternative Therapy Assessment).

Unaided Audiometric Threshold Levels

Unaided audiometric threshold levels will be obtained to determine if the participant meets inclusion criteria.

Air conduction threshold levels using insert earphones will be obtained at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. Masking will be used as necessary.

Bone conduction threshold levels will be obtained at 250, 500, 1000 2000, 3000, and 4000Hz in each ear. Masking will be used as necessary.

Verification of Hearing Aids

Participants will have their HAs assessed to ensure proper functioning and adequate amplification prior to testing. The American National Standard Institute S3.22-2009 for electroacoustic assessment will be used to ensure proper HA functioning. Amplification will be evaluated using real-ear measures with the AudioScan Verifit™ (or equivalent) system with speech stimuli for input levels of 50, 60 and 70 dB SPL. The evaluation will be based on the National Acoustic Laboratories' nonlinear fitting procedure, version 2 (NAL-NL2). If the participant's HAs do not meet NAL-NL2 targets within ±10 dB from 500-4000 Hz, the HAs will be re-programmed until targets are met. If the HAs cannot be adjusted to meet targets, the participant will be fit with clinic loaner HAs. If the severity of the hearing loss or tolerance issues prohibit amplification at the prescribed levels, the HA will be programmed as close as possible to NAL-NL2 targets.

Aided, FM Tone Sound Field Threshold levels

Aided, FM tone threshold levels will be obtained in the sound field for each ear at 250, 500, 1000, 2000, 3000, 4000, and 6000 Hz. When testing the poor ear, the better ear will be plugged and muffed (Howard Leight Pre-Shaped Foam Earplug and Howard Leight Hearing Protection Thunder T1 earmuff) (Howard Leight, 2014a, b). Based on pilot data from Washington University School of Medicine, the plug and muff provided an attenuation average of 48 dB for frequencies 250 – 8000 Hz.

CNC Word Recognition Testing

Two list of the CNC word test will be given to participants at 60 dB SPL in two listening conditions, 1) HA in the better ear only and 2) HA in the poor ear only. When testing the poor ear, the better ear will be plugged and muffed. Testing will determine if the participant meets inclusion criteria.

Alternative Therapy Assessment

Participants who have not previously failed a poor ear HA or BiCROS HA trial will be fit with one of those two HA options. The audiologist will determine which HA to fit based on the participant's hearing loss and preferences. After at least 1 to 2 weeks of use, the

participant will return to the center and complete an evaluation. Performance will be compared (using measures listed below) between the better ear HA-alone condition and the bilateral or BiCROS HA condition. If performance is better in the bilateral or BiCROS HA condition versus the better ear HA-alone condition, and the participant prefers the alternative therapy, the participant will not continue in the study. For participants who do continue in the study, these measures will not need to be repeated at the Pre-Implant Testing visit.

Sentence testing

Two lists of AzBio sentences will be administered at 60 dB SPL in 4-talker babble at +8 dB SNR.

Localization

CNC words will be presented through the eight loudspeaker array at a roved level of 65 dB SPL (±6 dB).

Candidacy Determination

The Investigator is required to submit the pre-operative candidacy evaluation CRFs for review by the Sponsor once the candidacy evaluation (when necessary, including the alternative therapy assessment) is complete. The information collected will be reviewed by the Sponsor, and a written approval or disapproval will then be provided to the Investigator. The Pre-Implant Candidacy Evaluation should take place within 4 months of surgery. Portions of the Candidacy Evaluation will be reassessed if more than 4 months have elapsed prior to the surgery date.

Pre-Implant Study Testing

The duration of this testing will be approximately 4 hours and will be completed in 1-2 visits. Pre-Implant study testing will be completed in the following three conditions: a HA in the better ear only, a HA in the poor ear only, and bilateral HAs.

Hearing Aid in the Better Ear

The participant will wear the HA and HA settings verified during the candidacy evaluation. If a loaner clinic HA was needed during the pre-implant candidacy evaluation, the participant will have worn this HA for at least 2 weeks prior to the pre-implant study testing. Participants will continue to use this HA for the remainder of the study.

Aided, FM Tone Sound Field Threshold Levels

Aided FM tone sound field levels will be obtained at 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz

Sentence testing

Two lists of AzBio sentences will be administered in quiet at a soft level of 50 dB SPL. Two lists of AzBio sentences will be administered at 60 dB SPL in 4-talker babble at +8 dB SNR.

Two lists of the BKB-SIN test will be administered in two listening conditions, sentences from the front loudspeaker and noise 90° to the participant's right and sentences from the front loudspeaker and noise 90° to the participant's left.

Localization

CNC words will be presented through the eight loudspeaker array at a roved level of 65 dB SPL (±6 dB). Localization will be completed in quiet and in the presence of restaurant noise.

Hearing Aid in the Poor Ear

When testing the poor ear alone, the better ear will be plugged and muffed.

The participant will wear the HA and HA settings verified during the candidacy evaluation.

Aided, FM Tone Sound Field Threshold Levels

Aided FM tone sound field levels will be obtained at 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz.

Sentence Testing

Two lists of AzBio sentences will be administered in quiet at a conversational level of 60 dB SPL.

Hearing Aid in Both Ears

CNC Word Testing

Two lists of CNC words will be administered in quiet at 60 dB SPL.

Sentence Testing

Two lists of AzBio sentences will be administered in quiet at a soft level of 50 dB SPL. Two lists of AzBio sentences will be administered at 60 dB SPL in 4-talker babble noise at +8 SNR.

Two lists of the BKB-SIN test will be administered in two listening conditions, sentences from the front loudspeaker and noise 90° to the participant's right and sentences from the front loudspeaker and noise 90° to the participant's left.

Localization

CNC words will be presented through the eight-loudspeaker array at a roved level of 65 dB SPL (±6 dB). Localization will be completed in quiet and in the presence of restaurant noise.

Questionnaires

HHIE

The HHIE will be completed by the participant. The HHIE will provide a baseline measure of the participant's perceived emotional and social/situational consequences of hearing loss.

HUI3

The HUI3 will be completed by the participant. The HUI3 will provide a baseline measure of the participant's overall health related quality of life.

SSQ

The SSQ will be completed by the participant. The SSQ will provide a baseline measure of the participant's perceived hearing ability in daily life.

SADL

The SADL will be completed by the participant. The SADL will provide a baseline measure of the participant's perceived satisfaction with amplification.

Participant Interview Form

The Participant Interview Form will be completed by the investigator after questioning the participant. This will provide a baseline for tinnitus, dizziness, medications and other relevant information.

Counseling

Along with the pre-implant candidacy evaluation and pre-implant study testing, participants will be seen by the surgeon and audiologist at their CI center for routine, clinical visits that occur prior to CI surgery. These visits will include discussions regarding the risks of CI surgery as well as performance outcomes with a CI to assure appropriate expectations.

Spouse/Significant Other – Pre-Implant Questionnaires

CPHI

The CPHI will be completed by the participant's spouse/significant other and will provide a baseline measure of the participant's communication in everyday life from the perspective of the spouse/significant other.

HII-SOP

The HII-SOP will be completed by the participant's spouse/significant other. The HII-SOP will provide a baseline of the perceived impact of the participant's hearing loss on the participant's spouse/significant other.

Surgery

Participants will be implanted with their selected CI device. The surgical procedure for implantation of each device will be according to each device's current approved labeling. Each surgeon will determine the length of participants' hospital stay based on their recovery. The following data will be obtained: date of surgery, device specifics and adverse event information.

Initial Stimulation of the Cochlear Implant

The initial stimulation of the CI will take place 2-4 weeks after surgery based on the surgeon's recommendation. Programming of each participant's CI speech processor will be performed according to each center's typical CI programming schedule. Selection of programming parameters will be determined by each center's routine, clinical procedures for optimizing CI recipient performance. At this visit the following will be obtained:

Unaided Audiometric Threshold Levels*

Air conduction thresholds using insert earphones will be obtained for each ear at 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz. Masking will be used when appropriate.

*If pre-implant, unaided audiometric testing reveals no response at each frequency in the poor ear, unaided audiometric testing in that ear does not need to be completed at this or any of the post-implant test sessions.

Participant Interview Form

The Participant Interview Form will be completed by the investigator after questioning the participant. This will provide information regarding tinnitus, dizziness, medications, the incision/implant site, and other relevant information.

Participants' take-home speech processor programs

The audiologist at each center will provide a de-identified copy of the speech processor programs. This will document relevant information regarding the parameters used by the participant with their speech processor.

Aural Rehabilitation

All participants will be encouraged by their audiologist to practice daily for 15-30 minutes listening with their CI only for at least the first 6 weeks of implant use and then 3 times a week for an additional 6 weeks. During practice, participants can listen with their CI through direct audio input to their CI or can listen through the CI alone by plugging the better hearing ear with an earplug. Each participant will be given a list of practice materials available for use on a computer, tablet, smart phone or through a CD player.

Post-Implant Study Testing (3, 6, 9 and 12 months after Initial Stimulation)

The duration of each session will be approximately 4-5 hours and will be completed in 1-2 visits. Audiometric, speech recognition, localization, self-assessment, speech processor program, and adverse event data will be obtained at each of the four post-implant test intervals. Post-implant test intervals should occur within a ± 30 day window around the target test date. Speech recognition and localization data will be obtained in multiple listening conditions as listed below.

Unaided Audiometric Threshold Levels*

Air conduction thresholds using insert earphones will be obtained for each ear at 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz. Masking will be used when appropriate

*If unaided audiometric testing at the initial stimulation reveals no response at each frequency in the CI ear, unaided audiometric testing in the CI ear does not need to be done at each post-implant test session.

Hearing Aid in the Better Ear

Verification of Hearing Aid

Each hearing aid will be checked for proper function and sound quality (e.g., listening check, electroacoustic analysis, patient report).

Aided, FM Tone Sound Field Threshold Levels

Aided FM tone sound field levels will be obtained at 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz.

CNC Word Test

Two lists of the CNC word test will be administered in quiet at a conversational level of 60 dB SPL.

Sentence Testing

Two lists of AzBio sentences will be administered in quiet at a soft level of 50 dB SPL. Two lists of AzBio sentences will be administered at 60 dB SPL in 4-talker babble noise at +8 SNR.

Two lists of the BKB-SIN test will be administered in two listening conditions, sentences from the front loudspeaker and noise 90° to the participant's right and sentences from the front loudspeaker and noise 90° to the participant's left.

Localization

CNC words will be presented through the eight-loudspeaker array at a roved level of 65 dB SPL (±6 dB). Localization will be completed in quiet and in the presence of restaurant noise.

Cochlear Implant Ear

Standard clinical procedures will be used to verify that the CI speech processor is functioning properly and the speech processor program is optimal prior to testing.

When testing the CI ear alone, the better ear will be plugged and muffed.

CI, FM Tone Sound Field Threshold Levels

CI, FM tone sound field levels will be obtained at 250, 500, 1000, 2000, 3000, 4000 and 6000 Hz.

CNC Word Test

Two lists of the CNC word test will be administered in quiet at a conversational level of 60 dB SPL.

Sentence Testing

Two lists of AzBio sentences will be administered in quiet at a conversational level of 60 dB SPL.

Bimodal (HA and CI together)

CNC Word Test

Two lists of the CNC word test will be administered in quiet at a conversational level of 60 dB SPL.

Sentence Testing

Two lists of AzBio sentences will be administered in quiet at a soft level of 50 dB SPL. Two lists of AzBio sentences will be administered at 60 dB SPL in 4-talker babble noise at +8 SNR.

Two lists of the BKB-SIN test will be administered in two listening conditions, sentences from the front loudspeaker and noise 90° to the participant's right and sentences from the front loudspeaker and noise 90° to the participant's left.

Localization

CNC words will be presented through the eight-loudspeaker array at a roved level of 65 dB SPL (±6 dB). Localization will be completed in quiet and in the presence of restaurant noise.

Questionnaires

HHIE: The HHIE will be completed by the participant at the 6-month post-implant study visit. The HHIE will record the participant's post-implant perceived emotional and social/situational consequences of hearing loss.

HUI3: The HUI3 will be completed by the participant at the 6-month post-implant study visit. The HUI3 will provide a post-implant measure of the participant's overall health related quality of life.

SSQ*:* The SSQ will be completed by the participant at the 6-month and 12-month post-implant study visits. The SSQ will provide a measure of the participant's perceived hearing ability in daily life with the CI and HA. The SSQ will be anchored for each of the post-implant test intervals; that is, participants will see how each question was answered at their previous test interval.

GBI: The GBI will be completed by the participant at the 6-month post-implant study visit. The GBI will document how the CI has affected the participant's health status and overall quality of life.

SADL

The SADL will be completed by the participant at the 6-month post-implant study visits. The SADL will provide a post-implant measure of the participant's satisfaction of the cochlear implant.

Participant Interview Form

The Participant Interview Form will be completed by the investigator after questioning the participant. This will provide information regarding tinnitus, dizziness, medications, the incision/implant site, and other relevant information.

Participants' speech processor programs used for testing

The audiologist at each center will provide a de-identified copy of the speech processor programs. This will document relevant information regarding the parameters used by the participant with their speech processor.

Spouse/Significant Other – Post-Implant Questionnaires

CPHI

The CPHI will be completed by the participant's spouse/significant other at the 6-month post-implant study visit. The CPHI will provide a post-implant measure of the participant's communication in everyday life from the perspective of the spouse/significant other.

HII-SOP

The HII-SOP will be completed by the participant's spouse/significant other at the 6-month post-implant study visit. The HII-SOP will provide a post-implant measure of the perceived impact of the participant's hearing loss on the participant's spouse/significant other.

Safety

A secondary objective of this study is to obtain data regarding the safety of cochlear implantation in adults with asymmetric hearing loss who receive a CI in the poor hearing ear and maintain a HA in the better hearing ear. The safety evaluation will be based on the number, type and degree of all adverse events.

A record of all adverse events will be kept. No formal statistical hypothesis will be tested. The primary safety endpoint will be 6 months post-implant. Adverse event information through 6 months post-implant will be summarized by event type, severity/seriousness, and whether related to the device and/or implant procedure.

Efficacy

The primary study objective is to obtain preliminary efficacy data in adults with asymmetric hearing loss who receive a CI in the poor hearing ear and maintain a HA in the better hearing ear. Efficacy is defined as post-implant improvement in the poor ear with a CI compared to pre-implant with a HA. Measures are sound field threshold levels and CNC monosyllabic words in quiet.

A secondary objective is to obtain efficacy data related to bimodal hearing. Efficacy is defined as post-implant improvement (CI in poor ear + HA in better ear) compared to the pre-implant best-aided condition (either HAs in both ears, or a HA in the better ear alone for adults with no aidable hearing in the poor ear). Measures are sound localization, speech recognition in noise, speech recognition at soft presentation levels, perceived hearing handicap, and reported quality of life.

Sample Size Justification

The primary efficacy endpoint is change in CNC performance from pre-implant to post-implant, with most of the gain expected to be achieved by 6 months. A clinically meaningful change on the CNC test is .10. In our past research we have found CNC standard deviations that range from .06 to .24. Assuming a correlation between repeated measures of .5 (typical in our work) these values translate into standardized mean differences (Cohen's d) ranging from .42 to 1.67. At the minimum effect size, a sample size of 37 is necessary for power of .80, the common standard (Cohen and Cohen, 1983; Keppel, 1991; Cohen, 1992). As indicated, the planned sample size will provide adequate to excellent power to detect clinically meaningful differences. Up to 40 participants will be enrolled to allow for attrition.

Note that the analyses described later will often be more complex than the simple approach used here for power calculations (a dependent means t-test), often involving change over longer periods of time, examining nonlinearity in the change profiles, and including additional predictors (e.g., patient characteristics). The impact of these modifications will generally be to increase power by including additional measures that

will make detection of change more sensitive or to include additional predictors that will reduce the error terms against which change is compared. We chose this simpler power analysis approach because it represents well the clinical meaning of improvement and is not complicated by extra statistical assumptions.

Data Analysis

Prior to the major analyses, the data will be examined for distributional abnormalities and outliers that might indicate the need for transformation to conform to the assumptions (e.g., multivariate normality) underlying the planned statistical procedures. When indicated, standard power transformations will be used to produce approximately normal distributions (e.g., (Tukey, 1977; Hamilton, 1992). If acceptable transformations are not available, resampling procedures will be used to confirm the conclusions drawn from the analyses. Resampling (e.g., Hamilton, 1992; Mooney and Duval, 1993; Chernick, 1999) represents a general statistical approach that bypasses possibly intractable assumptions necessary for the use of theoretical sampling distributions in favor of computer-intensive re-sampling of the obtained data to produce empirical sampling distributions for construction of confidence intervals. The approach is especially helpful when standard statistical approaches cannot be used with confidence and standard remedies (e.g., transformations) are not available.

Because of the longitudinal nature of the data, the major analytic approach we will use is hierarchical linear modeling (HLM; Raudenbush and Bryk, 2002; Heck and Thomas, 2009; Hox, 2010; Snijders and Bosker, 2012). We chose this approach because the data have a hierarchical structure, with the measures over time nested within individual patients. Thus for the majority of the analyses, we will use a two-level growth curve model, with both linear growth and quadratic growth (i.e., change in linear growth over time or departure from an overall linear or straight line pattern) included. HLM analysis is particularly well suited for longitudinal data with unequal spacing of measures and occasional missing data, both likely to be true in this study. Standard approaches, such as repeated measures analysis of variance, cannot be used because the measurement spacing will vary at the individual level. Missing data, which is not expected to be substantial, is handled in the HLM approach via maximum likelihood estimation (e.g., Enders, 2010). When HLM is used with smaller samples, standard errors may be reduced, although parameter estimates should not be biased (Raudenbush and Bryk, 2002). Accordingly, it may be necessary to use more conservative significance levels.

Estimation in the HLM approach is best thought of as occurring at different levels. At Level 1 of the statistical model, performance for a particular participant will be estimated as a quadratic polynomial growth curve. This can be described by the following model, using CNC performance as the example outcome:

$$CNC_{ti} = \pi_{0i} + \pi_{1i} Time_{ti} + \pi_{2i} Time_{ti}^{2} + e_{ti}$$

where the CNC performance at time *t* (e.g., six months) for participant *i* is estimated to be a function of an intercept (π_{0i}), a linear component for time (π_{1i}), and a quadratic component for time (π_{2i}). The coefficients are expected to vary systematically across patients. At Level 2 of the model, the coefficients from Level 1 are viewed as outcomes that depend on patient characteristics:

$$\pi_{0i} = \beta_{00} + \beta_{01}D_{1i} + \beta_{02}D_{2i} + \beta_{03}D_{3i} + r_{0i}$$
$$\pi_{1i} = \beta_{10} + \beta_{11}D_{1i} + \beta_{12}D_{2i} + \beta_{13}D_{3i} + r_{1i}$$
$$\pi_{2i} = \beta_{20} + \beta_{21}D_{2i} + \beta_{22}D_{2i} + \beta_{23}D_{3i} + r_{2i}$$

The three equations represent the intercept, linear component, and quadratic component of growth, respectively. The variables D_{1i}, D_{2i}, and D_{3i}, represent generic predictors such as dummy codes that could represent the particular center from which a patient's data were collected or patient characteristics (e.g., age) that might moderate the efficacy of the implant. These Level 2 predictors allow for systematic differences in patient performance to be detected.

The HLM approach includes omnibus tests that can be used prior to more focused comparisons so that the Type I error rate is not inflated. Judicious choice of centering the time variable allows targeted inferences about particular follow-up time-points. An important part of the HLM analysis are the diagnostic procedures to check assumptions (e.g., homogeneity of Level 1 variances) or to determine if models can be simplified (e.g., Level 2 residual variances of 0). When necessary, standard model modifications will be applied (e.g., modeling sources of Level 1 heterogeneity).

Some analyses will call for simpler approaches. For example, performance at particular measurement points will be of interest (e.g., at Pre-Implant, at 6 months Post-Implant, or at the conclusion of the study). In these simpler analyses, standard univariate and multivariate procedures (e.g., univariate or multivariate multiple regression [if continuous predictors are included] or analysis of variance [if only discrete predictors are tested]) will be used (Maxwell and Delaney, 1990; Keppel, 1991).

Risk Benefit Statement

The risks associated with CI surgery in this population are no greater than those associated with cochlear implantation in general. Cochlear implantation is an accepted treatment option for those with bilateral moderate to profound sensorineural hearing loss. However, the study population will have more residual hearing in the non-implanted ear and there may be an additional risk of sound interference when adding a CI with a contralateral HA. This will be monitored and recorded based on participant reports and comparison of performance between the HA-alone and bimodal conditions. Cochlear implantation is the only treatment option that can restore partial hearing to an ear with severe to profound hearing loss. It is well established that a CI can significantly improve audibility and speech understanding for individuals with postlingual onset of deafness. Individuals with SPHL in one ear and better hearing in the other ear may benefit from cochlear implantation by providing auditory stimulation in the poor hearing ear. Additionally, individuals with asymmetric hearing have the opportunity to benefit from HA use in the contralateral ear that has better hearing. Research has shown that bimodal hearing, a CI in one ear and a HA in the other ear, is well accepted by patients with residual hearing in the non-implant ear and is beneficial when listening to soft speech, listening to speech in noise and in localizing sound (Ching et al., 2007; Potts et al., 2009; Firszt et al., 2012; Morera et al., 2012; Dwyer et al., 2014). The potential to significantly improve speech recognition in the poor hearing ear, to improve understanding of soft speech and speech in noise, and to improve sound localization

suggests cochlear implantation of the poor ear may provide an acceptable risk-benefit ratio for individuals with asymmetric hearing loss as described in this protocol.

Good Clinical Practices Statement

The study will be conducted in compliance with federal standards of Good Clinical Practice, applicable government regulations and each investigational site's Institutional Review Board. Verification of IRB approval will be provided by each site to the Sponsor prior to study commencement. Any deviations from the protocol will be reported to the site's Primary Investigator and the institution's IRBs following each IRB's institutional guidelines.

Access to Study Documents and Monitoring

Research staff at the sponsor site will communicate with investigational sites at least quarterly to review study progress and assure the integrity of the accumulated data. On-site visits to the investigational sites will occur prior to study initiation and at least annually thereafter. Data generated by the study and the source documents will be open to inspection by the Sponsor, the FDA and other regulatory agencies.

Upon completion of the study, a representative from the Sponsor will conduct a final site visit to verify that all participants and their data are accounted for and that the regulatory records are complete.

Quality Control Assurance

Data will be provided to the Sponsor on case report forms. When CRFs are received, the forms will be reviewed to verify completeness and to identify inconsistencies or erroneous information. Corrections to the case report forms shall be made by approved methods only (i.e., single line through the incorrect entry, correct entry noted, initials of individual making correction, and date correction was made). The investigational site will be contacted to resolve any discrepancies in the case report forms.

Data received on CRFs will be entered into a database using typical data entry techniques. All data entry will be compared to the CRFs by someone other than the data entry research member. Samples of the CRFs received by the Sponsor and database entries will be compared with source documents during site visits to investigational sites. More comprehensive verification will be completed if deemed necessary.

Data and Safety Monitoring Board (DSMB)

The DSMB consists of three members, none of whom are directly involved in the research project: an otologist, a biostatistician and an audiologist with cochlear implant experience. The DSMB will review interim/cumulative data for evidence of study-related adverse events, efficacy, and data quality, compliance with recruitment goals, adherence to the protocol, and factors that might affect the study outcome or impact participant safety.

Institutional Review Board

Prior to study initiation at each investigational site, the IRB must have approved the Investigational Plan and the consent materials to be used. A copy of the approved investigational plan, consent materials and documentation of IRB approval for the study will be submitted to the Sponsor prior to participant recruitment and study initiation.

Informed Consent Process

An IRB approved investigator will be responsible for obtaining informed consent for each participant prior to initiating any study procedures. The consent process will include informing each participant of the study purpose, possible risks and potential benefits. These include the normal risks associated with general anesthesia, as well as other risks such as facial paralysis, dizziness, meningitis, postoperative discomfort, and flap complications. Potential participants will be given ample time to read the informed consent. Potential participants will be able to take the informed consent home to read and discuss study participation with friends and family. Individuals will be encouraged to ask questions. Once all questions are answered, both the participant and the investigator obtaining informed consent will sign and date the consent form. The original signed and dated form will be kept with the participant study records and a copy given to the participant.

Confidentiality

In accordance with Good Clinical Practices and with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), all information concerning study participants will be treated as confidential by all persons involved in the study. Each investigational site will follow the requirements of the site's IRB regarding confidentiality.

Data generated for the study will be stored in a limited-access file area and accessible only to study site research team members, the Sponsor, and FDA/relevant health authorities/regulatory agencies. All reports and communications with the Sponsor relating to study participants will identify participants only by a unique participant identification code. Full participant identification will be kept by the investigators at each investigational site.

Protocol Amendments

Protocol modifications that impact participant safety or study validity will be approved by the FDA prior to implementation. In addition, modifications will be documented in written form and approved by each investigational site's IRB prior to implementation. In the case of a medical emergency, to remove immediate apparent hazard to participants, a change may be made, preferably after discussion with the Sponsor. In these instances, the IRB and FDA will be notified as soon as possible.

Data Management

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded by the study investigator. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done (N/D) or the question was not asked, "N/D" will be written to indicate such. If the item is not applicable (N/A) to the individual case, "N/A" will be written next to the entry. All entries should be printed legibly.

If any entry error has been made, to correct such an error, a single straight line should be drawn through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. For clarification of illegible or uncertain entries, investigators will print the clarification above the item, then initial and date it.

Record Keeping and Retention

As described under Confidentiality, data generated for the study will be stored in a limited-access file area and be accessible only to each study site's research team members, the Sponsor, and FDA/relevant health authorities/regulatory agencies. All reports and communications relating to study participants will identify participants only by a unique participant identification code.

The Investigator must provide the Sponsor or designee with the following documents at the time of site qualification and prior to study initiation and retain a copy in the site study file:

- A copy of the original approval for conducting the study by the IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy and a copy of the approved and dated renewal provided to the Sponsor.
- A copy of the IRB approved informed consent form along with any modifications initiated by the Sponsor over the course of the study.
- The Investigator Agreement of this protocol signed and dated by the Primary Investigator from each site. In addition to the documents listed above, the study site will also retain the following items and make them available for Sponsor review upon request.
- Certifications and/or calibration records for applicable study equipment (audiometers, etc.). The Sponsor will verify all equipment requirements at the study qualification and/or initiation.
- All original informed consent forms with required signatures.
- Copy of the Study Monitoring Log.
- Copies of all correspondence pertaining to the study between Sponsor and the site.
- Copies of all case report forms submitted to the Sponsor.
- Site Delegation Signature Log.

All study-related records must be maintained for at least two years after study closure. The Sponsor will notify investigators at each site when records are no longer needed. The investigator will not discard any records without notifying the Sponsor.

Study Report and Publication

Neither the complete nor any part of the results of the study carried out under this protocol, or any of the information provided by the sponsor site for the purposes of performing the study, will be published or passed on to any third party without the consent of the Sponsor (via the study Principal Investigator, Jill B. Firszt). Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

At completion of the study, the compiled data will be analyzed and results shared with investigators from the investigational sites. Likewise prior to publication of results, the investigators from the investigational sites will be provided a copy of the accepted publication manuscript.

Adverse Events

Adverse Event (AE)

An AE is any unexpected medical occurrence or worsening of a pre-existing medical condition following implantation and exposure to the device, regardless of whether the AE is related to the surgery or device.

Adverse events (AEs) that occur during this study may be associated with the CI surgery, including AEs from general anesthesia, or specifically associated with the device use. An AE will be deemed device-related when, in the judgment of the study site's Primary Investigator, there is a logical connection between the device use and the event, above and beyond the study procedure itself.

Serious Adverse Event (SAE)

A SAE is any unexpected medical occurrence which:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization for more than 24 hours or prolongation of hospitalization which is not specifically required by the protocol
- Results in permanent impairment of a body function or permanent damage to a body structure
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Unanticipated Adverse Device Effect (UADE)

A UADE is "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." [FDA 21 CFR 812.3(s)]

Investigator Responsibilities

Throughout the course of the study, all efforts will be made to remain alert to possible AEs. Of primary concern will be the participant's safety and providing appropriate medical care. Detailed information regarding AEs will be recorded by the study site at

the time an AE occurs using the "*Adverse Event CRF*". All AEs will be recorded from the day of enrollment to the time when the participant exits the study or to study termination, whichever is the last, even if the event was acknowledged as a risk factor in the Informed Consent.

AEs will be recorded on the "*Adverse Event CRF*" and will include the following information:

- Date of onset
- Date reported to the clinic
- Description of the AE
- Seriousness (yes or no)
- Investigator's assessment of the relationship of the AE to the device
- Investigator's assessment of the relationship of the AE to the procedure
- Treatment
- Outcome
- Relationship to device, implantation procedure and/or underlying disease

A UADE will be reported directly to the study site's IRB and the Sponsor within 10 working days of learning of the event or as dictated by the study site's IRB, whichever is sooner. Information regarding the UADE will be recorded on the "*Unanticipated Adverse Device Effect CRF".*

Adverse Event Follow-up – Investigator Responsibilities

All AEs must be followed until resolution. The study site will follow-up as necessary with the participant to explain as well as possible the reason for and nature of the AE. This may include additional tests or consultation with other health care professionals. The Sponsor may request that the study site perform additional specific evaluations. AE follow-up information, as needed, will be recorded using a "*Previously Reported AE or UADE Follow-Up CRF".*

Adverse Event Follow-up – Sponsor Responsibilities

All AEs will be reported annually to FDA in accordance with the IDE regulation [FDA 21 CFR Part 812.150(b)(5)]. All UADEs will be reported to FDA within 10 calendar days of the event in accordance with FDA 21 CFR Part 812.46(b) and 812.150(b)(1). The Sponsor will notify all study sites of new safety information that alters the current risk-benefit assessment or that would be sufficient to consider changes in the overall conduct of the clinical trial.

Protocol Deviations

Any study-related activity not in compliance with the approved protocol is considered to be a protocol deviation. Deviations required to protect the life or welfare of a participant do not require approval and should be performed immediately. The IRB must be notified within 5 days of the event.

If a study participant is unable to return for a study visit within the allotted ± 30 day window around the target visit, or if a study visit is incomplete or otherwise completed incorrectly, these events will be tracked and logged. The Primary Investigator at each site will monitor this log and continually assess the nature and degree of these deviations to determine the impact of these events on safety or performance of the participant or data integrity.

Study Completion

Completed Participants

Participants are considered completed when all assessments through 12 months post-implant have been completed as mandated by the study protocol. Only participant data obtained with the originally implanted device will count toward the primary endpoint.

Discontinued Participants

Any participant can discontinue the study at any time without prejudice. The site's Primary Investigator may also discontinue a participant at any time if health is a risk or if the participant is uncooperative and otherwise impacting the integrity of the data. All withdrawals will be documented including the reason for withdrawal. Efforts will be put forth to ensure near complete follow-up, particularly on assessment of primary outcomes and occurrence of adverse events. Regular reminders, flexibility in scheduling of study visits to coincide with clinical visits, and close monitoring of due dates will facilitate obtaining as complete data as possible. Participants lost to follow-up will be contacted at least three times by phone, email or mail.

Premature Study Termination

Each study site reserves the right to discontinue the study for any safety, ethical or administrative reasons at any time. Participants who have already been implanted with the device will receive support, independent of study continuation.

Product Accountability

The three CI devices commercially available in the United States will be used during the study. The devices are manufactured by Advanced Bionics, LLC (PMA P960058/S089/S098/S102), Cochlear Americas (PMA P970051/S028/S064/S096), and Med-EL Corporation (PMA P000025/S023/S029/S050/S061/S077). All devices are commercially available and ship with their current commercial labeling.

Because these devices are commercially available, no investigational labeling is included.

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