A PROPOSAL TO EVALUATE REVISED INDICATIONS FOR COCHLEAR IMPLANT CANDIDACY FOR THE ADULT CMS POPULATION

(CMS-ERID)

PROTOCOL
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SUBMITTED ON BEHALF OF THE AMERICAN COCHLEAR IMPLANT ALLIANCE

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EVALUATION OF REVISED INDICATIONS FOR ADULT COCHLEAR IMPLANT CANDIDACY

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CLINICAL INVESTIGATIONAL SYNOPSIS

Title	**Evaluation of a Revised Indication for Determining Adult Cochlear Implant Candidacy**
Study Sites	Up to 10 North American centers
Study Duration	24 Months
Study Time	12 months post-activation for each study participant
Study Population	Up to 90 adult participants with post-lingual onset of hearing loss
Design Overview	The study will be conducted as a repeated-measure, single-arm design.
Objectives	1) To evaluate the safety and efficacy of currently available multichannel cochlear implant systems for newly implanted adults with an indication based on open set sentence recognition that expands criteria currently used by CMS 2) To assess the correlation between measures of speech recognition in candidates for cochlear implants and their utility in predicting audiologic and quality of life outcomes after implantation
Study Intervals	Preoperative candidacy Baseline measures Surgical questionnaire Post-activation evaluation at 6 and 12 months
Primary End Points	Report of safety and clinical performance 12 months post-activation using multichannel cochlear implant systems in newly implanted adult populations
Secondary Outcomes	Self-rated quality of life as reflected in utility measures

DEFINITIONS AND ABBREVIATIONS

Terms/Abbreviations	Definition
AzBio	The AzBio sentences were developed at Arizona State University by a grant provided by the Arizona Biomedical (AzBio) Institute. The sentences are comprised of 33 lists containing 20 sentences each. Each list presents 2 male and 2 female talkers each providing 5 sentences. Information regarding the development and equivalency of AzBio sentences may be found in Spahr et al., 2011.
CNC	Consonant-Vowel Nucleus-Consonant (CNC, Peterson & Lehiste, 1962) test consists of 10 lists of monosyllabic words. Each list contains 50 stimuli. The test is scored as number of words and phonemes correct.
Preferred sound processor program	Speech processor program most often used by the participant in everyday settings
dB(A)	Refers to the A weighted scale selected on the sound level meter when calibrating test measures.
MAP	A speech processor program that defines the psychophysical parameters (e.g., electrode settings for soft and comfortable loudness, frequency allocations, speech coding strategy) for an individual participant.

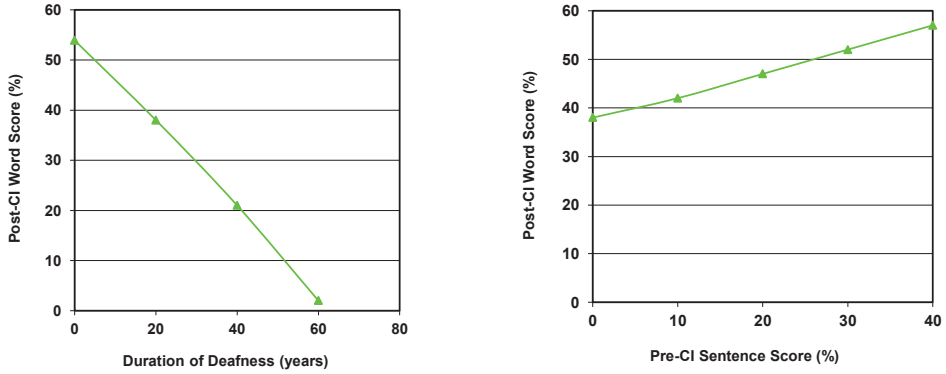
INTRODUCTION

We value the progression of hearing healthcare practices and technology and acknowledge a need for critical, ongoing evaluation of indications for determining cochlear implant candidacy in adult populations. This need arises from gaps identified within the body of current research knowledge evident in the peer reviewed literature. Specifically, technological advancement with concomitant performance outcomes should be critically assessed. In no population are such evaluations more critical than in our expanding population of older adults. Seniors and other populations face significant communication disabilities and negative life impact when hearing loss is so advanced that it limits the benefit derived from traditional amplification. However, intervention with a surgical treatment in this population must be conducted with due caution and focus on critical evaluation of benefit using both disease-specific (audiometric) and generic, health-related quality of life measures.

The CMS-eligible patient population is uniquely positioned to offer research insights into the level of benefit derived from cochlear implantation as a function of pre-implantation indicators. Currently, a maximum pre-operative sentence score of 40% serves as a criterial boundary for cochlear implant candidacy. As we describe below, this current indication for implantation may be vulnerable to error in predicting potential benefit from cochlear implantation in a portion of the CMS-eligible population.

To analyze the benefits from cochlear implantation in this population, we have reviewed studies that have applied multivariable statistical models in adult cohorts that are substantially (>50%) populated by seniors 65 years & older. Though a wide array of factors were analyzed in these models (including age at CI, age at onset of hearing loss, cause of hearing loss, duration of hearing aid use, gender, ear implanted, pre-operative hearing scores, and particular device used by the participant), the duration of deafness and pre-operative sentence scores of subjects were consistently found to be the two most significant predictors of postoperative hearing outcomes (Fig. 1) (Rubinstein et al. 1999).

Figure 1. Graphs the model observations that postoperative word recognition scores decrease as preoperative duration of deafness increases, and that higher postoperative sentence scores obtain in implant recipients with higher preoperative sentence scores.



The resulting models (from Rubinstein et. al., 1999) of post-implantation outcomes follow a similar mathematical structure with a study participant's post-operative word score starting at a constant value **k** which is either increased by the addition of a term dependent on the pre-CI sentence score or decreased by the subtraction of a term dependent on the duration of deafness:

Predicted % of words in everyday sentences =
k - (**Dur** Yrs df) + (% words **Pre-CI**)

Further development of predictive models (Roditi et al., 2009; Leung et al., 2005; Friedland et al., 2004) have shown that for adults, age at implantation carries minimal, statistically-insignificant predictive power on post-implantation outcomes. Rather, minimizing duration of deafness and implanting individuals with higher pre-operative sentence scores yields better post-implantation outcomes across the entire adult population.

Importantly, the 65 and older population is more likely to suffer from late onset hearing loss and less from congenital or pre-lingual causes of deafness than patients less than 65 years of age, resulting in a shorter duration of deafness (Leung et al., 2005). Thus, this population benefits from an increased duration of experience with auditory-oral language than a younger group of adults with hearing loss. With the duration of deafness held equal, this finding is more likely to result in higher pre-operative sentence scores and, therefore, greater benefits from implantation for the elderly population.

Though statistical significance was not reached in the below-65 cohort, these findings show that senior populations stand to benefit at least as much, if not more than the younger adult population. To this point, data from the above studies indicate that the use of a ratio of duration of deafness to the age at implantation points to a more significant factor in determining post-implantation word scores. A higher ratio that reflects prolongation of periods of auditory deprivation associates with diminished post-operative perception of the spoken word. Conceptually, such correlations suggest that preserving a foundation of central auditory processing through effective signal transmission to auditory nuclei along the central nervous system is critical to speech recognition after cochlear implantation. Thus, waiting for a patient's speech recognition score to decrease until he/she meets current candidacy criteria may result in poorer post-operative performance.

Preliminary Studies

A pilot study was pursued to accrue data that would inform this present proposal. We asked 9 active implant centers to provide data from recipients 65 years of age and older who demonstrated a pre-operative HINT score that fell between 41 and 60% correct in the best aided condition within one year prior to receiving a cochlear implant. Recruited data reflected study participants who progressed in their hearing loss to demonstrate a score of $\leq$40% (thus meeting CMS guidelines

for implantation), recipients who received their implant because they participated in a manufacturer-funded trial, or international and other self-paying participants.

Post-operative scores obtained from 79 implant recipients accrued from 9 different centers provide an estimation of the size of the clinical effects we would expect to see in the over-65 population selected based on pre-implantation HINT scores that ranged from 41-60% in the subject's best aided condition. The study population had a mean age at implant of 73.4 years (age ranged from 61-89 years), had a mean pre-implantation HINT score of 48.4% (range = +/-7.5%), and a mean post-operative HINT score of 80.9% (range = +/- 19.2%). This resulted in an average gain of 32.5% on HINT sentences. The table below compares findings of this pilot data set to other studies of adult subjects (with lower mean pre-operative scores) across the age spectrum.

Parameter (SD)	Bradley	Bassim	Lustig	Roditi	Pilot Data
Mean Age at CI	50 (15.3)	54 (19.0)	61 (15.5)	62 (15.3)	73 (6.9)
Preoperative HINT	15 (17)	4 (NA)	28 (29)	9 (14)	48 (7)
Postoperative HINT	81 (25)	87 (NA)	78 (41)	66 (30)	81 (19)
Delta	66 (22)	83 (NA)	50 (37)	57 (25)	33 (16)

Note that the mean postoperative score is not dissimilar to that seen in younger study populations. Though pre-implantation HINT scores are positively predictive of post-implantation outcomes, the 33% sentence score gain in the pilot study of older subjects was lower than that seen in models with younger populations. This difference is largely explained by ceiling effects in the HINT metric, given that a substantial proportion of the pilot population has reached post-operative HINT scores greater than 90%. This finding illustrates limitations of the HINT metric and is discussed in the context of alternative measures designed to overcome HINT ceiling effects.

Since 1998, adult cochlear implant indications have transitioned from a bilateral profound sensorineural hearing loss with 0% open set sentence discrimination to the current criteria set forth in 2005 (PMA # P970051/S028). Current indications include individuals with bilateral moderate to profound sensorineural hearing loss who demonstrate limited functional benefit from amplification defined by scores of $\leq$50% using open set sentence recognition in quiet in the ear to be implanted and $\leq$60% in the best-aided condition.

In parallel with evolving indications, the speech recognition measures used to establish candidacy have also undergone transition. In 1996, a committee formed of representatives from the American Academy of Audiology (AAA), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), and cochlear implant manufacturers met to develop the original Minimum Speech

Test Battery (MSTB) for Adult Cochlear Implant Users. This battery was designed to identify a set of materials for determining audiologic implant candidacy and for evaluating postimplant performance. They proposed use of the HINT sentence measure as a means to move away from use of the much easier CID Everyday sentences (Davis and Silverman, 1978).

In 2001, the MSTB recommended use of HINT sentences postoperatively to assess performance in an adaptive approach with a fixed-level noise to determine the SNR required for 50% correct in an effort to avoid ceiling effects (Luxford et al. 2001). Despite a recommendation for the use of HINT in an *adaptive* approach, current labeling and a majority of hearing care specialists utilize HINT scores obtained in quiet and do not employ a signal-to-noise ratio for determination of adult implant candidacy. However, much like the CID Everyday sentences that were used previously, HINT sentences do not adequately allow for longitudinal assessment of performance owing to a large proportion of individuals exhibiting ceiling values. Such limitations can affect both post-implant and pre-implant scores (Gifford et al. 2008).

The aforementioned sentence recognition measures, CID Everyday and HINT sentences, have continued to be evaluated and documented as inappropriate test measures, thus advancing a significant need for revised indications. Gifford *et al.* (2010) concluded that a larger scale re-assessment of manufacturers' preoperative candidacy criteria for adults (both the FDA and Medicare-approved criteria) was warranted in order to more accurately predict which hearing-impaired individuals would benefit from cochlear implantation. Gifford et al. (2008) examined the appropriateness of speech recognition materials based on preimplant and postimplant assessment of performance. Monosyllabic word (CNC), sentences in quiet (HINT, AzBio) and in noise (BKB-SIN) were evaluated retrospectively in 156 adult, postlingually deafened implant recipients and 50 hearing aid users. Mean duration of cochlear implant use was 45 months (range 3-198 months). Results revealed a notable ceiling effect for HINT sentences in quiet; 28% of the implant recipients tested achieved a score of 100%; 71% of the population achieved scores greater than 85%. The other speech perception measures used in the Gifford 2008 study, CNC words, AzBio sentences in quiet and BKB-SIN sentences in noise were found not to suffer from ceiling effects. Of the 206 subjects evaluated, only one subject (0.7%) achieved a score of 100% on AzBio sentences; none achieved 100% performance on CNC words. Gifford et al. concluded that the HINT sentences in quiet are not appropriate for tracking performance over time, nor may they be appropriate for determining implant candidacy (Gifford et al., 2008). This conclusion has also been documented in peer reviewed studies of individuals with hearing levels in excess of the current guidelines; implant recipients with significant sentence recognition scores greater than 50% correct are now receiving a cochlear implant with documented benefit (Adunka et al., 2008; Novak et al., 2007; Gifford et al., 2007, 2010; Cullen et al., 2004).

A consensus in the peer reviewed literature suggests that HINT sentences (in quiet) fail to offer a valid assessment in determining implant candidacy and in evaluating post-operative speech performance. Changes in the technology and its application—improvements in speech coding strategies, front-end processing, and surgical techniques--have occurred since the initial approval of the multi-channel cochlear implant in 1985 (PMA# P840024). With these advances, improvements in cochlear implant recipient performance have also been observed (Gifford et al., 2008; Firszt et al., 2004; Alkaf & Firszt, 2007; Litovsky et al., 2006; Luxford et al., 2001). In order to capture and track performance, more difficult test metrics are required to obviate the inevitability of ceiling effects.

In this study, we propose to collect data using AZBio sentences in quiet to remain consistent with procedures most recently used by clinics to determine candidacy for a cochlear implant. We additionally propose to collect CNC monosyllabic word scores in order to evaluate the utility of these materials for improved determination of implant candidacy.

In consideration of a revised indication for cochlear implants, the impact on ease of communication and quality of life should also be addressed. In an effort to investigate this aspect further, we propose to evaluate speech understanding in everyday life and impact on quality of life using the validated Abbreviated Profile of Hearing Aid Benefit (APHAB) (Cox & Alexander, 1995), Short Form-36 (Ware, 1993), and Health Utility Index (HUI3) (Furlong, W., Feeny, D., Torrance, G.W., Barr, R.D., 2001) Questionnaires. The APHAB is useful for quantifying the disability associated with a hearing loss (Cox & Alexander, 1995). The SF-36 questionnaire can be used to derive a preference-based health utility index through the application of utility transforms. This derived index has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. The Health Utility Index (HUI) systems were developed to integrate fully descriptive classification information about disability with preference based measures of importance and provide a comprehensive description of the health status of subjects in clinical studies (Furlong et al., 2001).

Changes in severity of co-morbid states or appearance of new and significant medical conditions can affect results obtained on the quality of life scales used in this study. The results of the SF-36 will help determine if any new or significant medical conditions have taken place during the course of this study (related or unrelated to the CI) that may affect the results.

Summary
Due to the limitations of the current candidacy criterion in appropriately identifying those in need of a cochlear implant, modified approaches to candidacy assessment need to be implemented. Because materials such as HINT sentences (in quiet) fail to discriminate those listeners at risk for poor

speech recognition in real world settings, current candidacy criteria based upon HINT sentence scores are likely set too conservatively.

We believe it is time to re-evaluate the candidacy requirements associated with adult cochlear implantation. This is supported by recent peer reviewed literature illustrating a need for an appropriate criteria and more suitable speech recognition measures. Specifically, this will be accomplished by evaluating the benefits of cochlear implantation in CMS-eligible adult patients with pre-implantation AZBio (in quiet) sentence scores that fall in the 41-60% range. Secondly, this CMS-sponsored study provides the opportunity for key corollary data collection that examines the use of test materials that are more reflective of the communication demands of real world settings faced by the CMS population. Thus, in this study we propose the deployment of readily accessible test metrics designed to overcome the ceiling effects and limitations of the HINT sentences test (in quiet). Thus, this study includes the additional test measure of CNC words.

KEY PERSONNEL

PRINCIPAL INVESTIGATORS

Three cochlear implant clinician-scientists will share principal investigator responsibilities for this project. This is based on their vast experience working with cochlear implant recipients and their experience leading and participating in multi-center trials. The co-principal investigators are geographically diverse, residing in California, Michigan, and North Carolina. Curriculum vitaes for the three principal investigators may be found in Appendix C.

Teresa A. Zwolan, Ph.D. is a Professor and Director of the Cochlear Implant Program in the Department of Otolaryngology at the University of Michigan. She will oversee the audiological aspects of this study, including training and instruction of participating audiologists, and oversee data collection related to audiological outcomes. Dr. Zwolan will assist with submission of study findings to CMS and will also participate in manuscript preparation following completion of the study. Dr. Zwolan will serve as the primary contact person for this study with CMS.

Craig Buchman, MD is a Professor and Chief, Division of Otoloty/Neurotology and Skull Base Surgery at the University of North Carolina. Dr. Buchman will oversee the work of Popsicube, Inc., (www.popsicube.com) a Clinical Research Organization (CRO) that has been selected for this study to assist with site management, data capture, and statistical analyses. Dr. Buchman will also assist with submission of study findings to CMS and will also participate in manuscript preparation following completion of the study.

DATA MANAGEMENT

Popsicube, Inc., a Clinical Research Organization (CRO) has been selected to assist with data management for this study (www.popsicube.fr/). They were selected based on their experience developing and implementing a nationwide cochlear implant registry in France in 2011. They will assist with all aspects of the study related to data management, including data capture and entry, center training, randomization of test lists, data/query management, data export, codification, statistical analysis, clinical report, and preparation of data for publication. Key personnel from Popsicube assigned to this project include Bruno Scherrer, Ph.D, M.B.A. (consultant in methodology and biostatistics) and Rodolphe Merrina, (Biostatistician and Data Manager). Both of their CVs are attached.

Additional statistical support will be provided by the Universities of the respective Principal Investigators: The University of Southern California, The University of North Carolina, and The University of Michigan.

STUDY OBJECTIVES

PRIMARY OBJECTIVES

The primary objective of this multi-center study is 1) to evaluate the safety and efficacy of currently available multichannel cochlear implant systems for newly implanted adults with an indication based on open-set sentence recognition that expands criteria currently used by CMS, and 2) to assess the correlation between measures of speech recognition in candidates for cochlear implants and their utility in predicting audiologic and quality of life outcomes after implantation

INVESTIGATIONAL METHODS

PROFESSIONALS INVOLVED IN THE STUDY

Surgeons: Surgeons who participate in this study will be required to be a board certified otolaryngologist-head and neck surgeon by the American Board of Otolaryngology. At the request of CMS, each surgeon involved in this study will complete a questionnaire that will provide information regarding the number of cochlear implant surgeries performed by that surgeon during the previous 12 months, and if the surgeon is fellowship trained in neuro-otology. At the time of surgery, the surgeon will complete a surgical questionnaire that will include indication of the surgical approach used to access the cochlea, the type of device implanted, and information regarding if intra-operative steroids were applied, in addition to other information.

Audiologists: Audiologists who participate in data collection or patient management for this study will be required to hold a current license to practice audiology in the state where their cochlear implant center is located. This will ensure that all audiologists will have met their state's continuing education renewal requirements that must be met to stay licensed. Presently, states require audiologists to have either a master's degree or an Au.D. degree to obtain their audiology license. Minimum requirements for the Au.D. degree include a minimum of 75 semester hours of post-baccalaureate study, meeting prescribed competencies, passing a national exam offered by Praxis Series of the Educational Testing Service, and practicum experience that is equivalent to a minimum of 12 months of full-time, supervised experience. At the request of CMS, each audiologist involved in this study will complete a questionnaire that describes the type of specialized training he/she has received in the evaluation and treatment of cochlear implant recipients. He/she will also indicate the number of patients that he/she has been the lead audiologist for during the previous 12 months.

Speech-language pathologists (SLPs) are not directly utilized in this study. However, there is a recommendation regarding when professionals should refer a participant to an SLP for additional aural rehabilitation and training. The participant should be referred to a speech-language pathologist who has

experience performing aural rehabilitation and training with adults who have severe to profound hearing loss.

Centers will be asked to verify that the surgeon(s), audiologist(s), and speech language pathologist(s) involved in this study meet the above mentioned criteria prior to the clinic's official enrollment in the study.

SELECTION OF STUDY PARTICIPANTS

The proposed investigation is designed to include up to 90 adult study participants implanted at up to 10 study sites within North America.

Clinics will be instructed to ask each patient who qualifies for the study to consider enrolling in the study. In addition to the stated audiologic criteria, all subjects will be 65 years of age or older at the time of the study and CMS-eligible as their primary source of medical insurance coverage. This will foster inclusion of all possible subjects and will help prevent selection of "optimal" subjects for this study.

The expected duration of this multi-site study is 24 months. The anticipated duration of individual participation is expected to be 12 months from implantation.

Criteria for Inclusion

- Sixty-five years of age or older at the time of the study and CMS-eligible as primary source of medical insurance coverage.
- Bilateral moderate to profound hearing loss in the low frequencies (up to 1000 Hz) and profound sensorineural hearing loss in the high frequencies (3000 Hz and above).
- Preoperative aided sentence score in quiet greater than or equal to 40% correct but less than or equal to 60% correct in the best aided condition on recorded AzBio sentences.
- English spoken as the primary language.

Criteria for Exclusion

- Congenital hearing loss (for the purpose of this study, onset prior to 2 years-of-age).
- Preoperative aided sentence score less than 40% or greater than 60% correct in the best aided condition on AzBio sentences in quiet

- Ossification, absence of cochlear development or any other cochlear anomaly that might prevent complete insertion of the electrode array.

- Hearing loss of neural or central origin (e.g., deafness due to lesions on the acoustic nerve or central auditory pathway).

- Active middle-ear infection.

- The audiologist and/or surgeon will review the study protocol with the patient prior to having him/her sign the consent form. If the patient indicates he/she is unwilling or unable to comply with all investigational requirements, he/she will not be enrolled in the study.

- Using best clinical judgment based on professional interaction with the patient and his/her family, the managing audiologist and surgeon will determine if there are any disabling cognitive limitations that would prevent the patient from providing reliable data for this study.

Evaluation Materials

All tests and distribution lists will be randomized (without replacement of the pre-implant test when performing post-implant testing) to reduce the potential for learning effects. Information regarding set up for testing may be found in Appendix A. Sample test lists and score sheets for outcome measures used in this study are provided in Appendix D.

Speech Test Descriptions

Consonant Nucleus Consonant (CNC) Monosyllabic Word Test (Peterson & Lehiste, 1962)
CNC Word Test is a validated test of open-set word recognition. The test consists of 10 lists with 50 monosyllabic words in each list. The test consists of recorded stimuli presented by a single male speaker. Participant responses are scored for both words and phonemes correct in the correct sequence. Study participants will be tested using a configuration of one complete list presented at 0º azimuth in quiet.

AzBio Sentences Test (Spahr et al., 2011)
The AzBio Test is a validated test that consists of 33 lists of 20 sentences each. All sentences are recorded and each list includes 5 sentences from each of 2 different male and female speakers. The average level of intelligibility of each list for listeners with normal hearing is 85% +/- 1%. These performance data are

reflective of the heightened stringency of this speech recognition test, thus enabling the ERID Trial to overcome the ceiling effect suffered by HINT testing in quiet. Each word in the sentence counts towards the overall score. Participants will be tested using a configuration of one complete list per condition and stimuli will be presented at 0º azimuth in quiet.

All of the speech recognition measures described above will include taped materials presented to a soundfield in quiet at a level of 60 dB SPL. Stimuli will be presented a single time only and feedback will not be provided.

Self-Assessment Questionnaire Descriptions

The Abbreviated Profile of Hearing Aid Benefit (APHAB) (Cox & Alexander, 1995) The APHAB is a 24-item self-assessment scored in four subscales (6 items per subscale). Three subscales: Ease of Communication, Reverberation, and Background Noise, address speech understanding in everyday life. The fourth subscale, Aversiveness to Sounds, measures negative reactions to environmental sounds. Form A of the questionnaire will be administered as recommended by the authors of the APHAB questionnaire. The APHAB has been shown to be useful in assessing communication ability in cochlear implants across a spectrum of ages and baseline hearing levels (Plyler et al, 2008; Donaldson et al, 2009; Gstoettner et al, 2011).

Short Form-36 (SF-36) Questionnaire (Ware et al. 1993)
The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index using utility transforms (Brazier et al. 2001). It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. Thus the SF-36 offers an estimate of utility in a highly subject-friendly format that captures utility measures to be probed in parallel with the Health Utility Index Mark 3. The SF-36 has been shown to be a useful metric of generic health as it relates to communication ability in cochlear implant recipients across a spectrum of ages and baseline hearing levels (Hirschfelder et al, 2008; Damen et al, 2007). The results of the SF-36 will help determine if change in severity of co-morbid states or appearance of new and significant medical conditions affects the results obtained on the quality of life scales administered during this study.

The Health Utility Index Mark 3 (HUI-3) (Furlong, W., Feeny, D., Torrance, G.W., Barr, R.D., 2001). Prior data have correlated utility measures with speech recognition gains as reflected in HUI3 results. The HUI3 survey will be administered at baseline and post-activation. The HUI-3 has been shown to be a useful metric of health-related quality of life as it relates to communication

ability in cochlear implant recipients across a spectrum of ages and baseline hearing levels (Palmer et al, 1999; Lee et al, 2006; Damen et al, 2007).

INVESTIGATIONAL PROTOCOL

The study will be conducted as a repeated-measure, single-arm design. This approach, in which each participant serves as his or her own control, is appropriate since it accommodates the heterogeneity that characterizes hearing-impaired populations. Blinding or masking procedures are not included because it is not possible to conceal the presence or absence of a cochlear implant from device recipients or clinical investigators.

Procedures for speech test setup, calibration and administration are included in Appendix A.

Preoperatively, candidates will participate in unaided audiological testing and aided speech recognition testing using appropriately fit hearing aids. Speech recognition tests will be administered pre-operatively to evaluate appropriateness for enrollment into the study, and to establish baseline measures.

Postoperatively, study participants will return at 6 and 12-month post-activation test intervals for speech recognition testing and for administration of questionnaires. Participants may be evaluated between test intervals as directed by their managing audiologist and as dictated by the implanting center's protocol for such testing. During follow-up postoperative evaluations, if an adverse event is experienced, the Principal Investigator is required to complete an adverse event form and submit it to the Study Coordinator and to notify their IRB.

Preoperative Procedures

Informed Consent

Prior to enrollment in the study, an interview with the potential candidate will be conducted to discuss study expectations, potential risks and benefits as well as the study evaluation schedule. The Informed Consent Form may be taken home and reviewed by the candidate. After reviewing the form, the candidate will be given the opportunity to ask questions about it and/or the study prior to signing the form. The candidate will then be given a copy of the signed Informed Consent Form. The Informed Consent Forms will include a detailed list of procedures the subject should have participated in as part of the pre-operative evaluation process.

The Informed Consent document will be reviewed and signed by the relevant parties prior to any study-related evaluation taking place. Testing completed as part of normal clinical practice, such as the audiogram is acceptable.

Hearing History

Information regarding each participant's hearing history (etiology and onset of hearing loss; duration of severe-profound loss; previous amplification use, history of tinnitus and vertigo/dizziness) will be collected and reported on a data collection form. This information may be obtained either from the participant directly or from their medical record.

Preoperative Evaluations

The Preoperative evaluation has two components:

1. Assessment of the candidate's suitability for the study, and
2. Establishment of baseline data should the candidate prove to be appropriate for study inclusion.

During the aided conditions in the preoperative assessment, the patient will utilize hearing aids that have been verified as appropriate by the participant's managing audiologist. Clinicians will be instructed to base the appropriateness of the hearing aid fitting on the recommendations published by the American Academy of Audiology Task Force (2006). This includes real ear measures to verify accuracy of the hearing aid settings.

Candidacy Assessment

- Air conduction thresholds with insert earphones at 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000Hz
  - Unilateral, each ear

- Bone conduction thresholds at 125[1], 250, 500, 750, 1000, 1500, 2000, 4000Hz
  - Unilateral, each ear

- AZBio Sentences Test (Quiet) – One complete recorded lists at 60 dB(A) presented to the soundfield in three conditions while the patient utilizes amplification that has been verified as appropriate by the participant's managing audiologist
  - Right ear aided, left ear aided, bilateral aided

Baseline Measures

Speech Perception Testing

- CNC Word Test (Quiet) – One complete recorded list presented at 60 dB(A) in three aided conditions:
  - Right ear aided, left ear aided, bilateral aided

Telephone Testing will be performed using the same test conditions pre-implant and 6 and 12 months post-implant

[1] Bone conduction measures at 125 Hz are recommended if there are no audiometric equipment limitations.

- Two lists of CUNY Sentences will be administered via live voice by the managing audiologist. The participant will couple the ear to be implanted to his/her hearing aid with the settings typical for phone use by that participant. If the participant is unable to use the phone, the test will still be administered with the telephone placed over the hearing aid microphone. No additional assistive listening devices (i.e. handset amplifier) or speaker phone settings will be used. Stimuli will be presented a single time only and feedback will not be provided. The examiner will use a conversational level and rate and will present each sentence via live voice over the phone. After each sentence is read, the participant will repeat as much of the sentence as possible, guessing when necessary. Correct and incorrect responses will be recorded by the examiner. Sentences will be scored for number of words repeated correctly and a percent of total words correct will be calculated. See Appendix D for additional information.

Self-Assessment Questionnaires: Patients will be instructed to complete the questionnaire as it pertains to how they presently hear in everyday listening situations:

- Health Utility Index (HUI3)
- SF-36 with utility transforms
- APHAB Form A

Surgical Procedure

The recommended surgical procedure as outlined in the appropriate surgical manual for the device selected for implantation (provided by the device manufacturer).

- The surgeon is required to complete following each surgery:
  - A surgical questionnaire (see Appendix D)

Postoperative Procedures

Post-operative management of cochlear implant recipients must be tailored to the needs of the patient, and will vary depending on the type of cochlear implant the patient receives. Recommended procedures for audiologists who manage patients enrolled in this study are provided below:

Post-operative mapping recommendations

-Activation should take place 2-4 weeks following surgery, or as soon as the surgeon has determined that the patient is able to participate in such an appointment.

Activation procedures (performed by the audiologist)

-Check incision site for signs of irritation or infection. Perform otoscopy. Refer patient to CI surgeon if there are concerns.

-Check adhesion of the speech processor magnet to ensure appropriateness of magnet strength. Increase or decrease magnet strength as needed.

-Perform listening check of speech processor microphone.
-Perform impedance testing (Telemetry)

The following **mapping parameters** are recommended as defaults to begin with, but may be modified as needed based upon the recipient's response to sound:

Nucleus Device:
Processing strategy: ACE
Stimulation Mode: MP1+2
Rate: 900 Hz
Maxima: 8
Pulse width: 25us

Advanced Bionics
Processing Strategy: HiRes-S w/Fidelity 120
Pulse Width: APWI 18.0 us
Channel Rate: 3712
IDR: 60

MedEl
Processing Strategy: Fine Structure Processing (FSP)
Stimulation Rate: Begin with maximum available stimulation rate
Pulse Width: Software default
CSSS channels: Use to maximize the number of CSSS channels
Frequency Bands and Maplaw: Logarithmic
AGC Compression ratio: 3:1

Recommended schedule of appointments:
The scheduled follow up appointments for recipients will vary depending on the recipient's response to sound, clinic schedule, and distance traveled to the clinic by the recipient. In addition to device activation, it is recommended the audiologist try to meet with patients during the following intervals:
One month post-activation
Three months post-activation
Six months post-activation (formal testing to be performed during this appointment per study protocol)
Twelve months post-activation (formal testing to be performed during this appointment per study protocol)

Each mapping appointment should include the following:
-Discussion of experience using the device and clarification of any questions regarding device use
-Listening check of speech processor microphone
-Impedance telemetry
-Assessment of thresholds and comfort C or M levels
-Loudness balancing of C or M levels

-Creation of new speech processor programs if levels have changed
-informal assessment of speech recognition using the attached guide that includes
-Identification of numbers ranging from 1-100 (randomly administered) using hearing alone.
-Identification of colors (randomly administered) using hearing alone
-Identification of open set informal sentences

Patients should be referred to a speech-language pathologist for formal aural rehabilitation/training if:
-At the three month interval he/she demonstrates no open-set speech recognition of numbers, colors, or sentences.
-the recipient demonstrates difficulty adjusting to the sound quality of the cochlear implant
-If there is a question regarding the presence of coexisting communication difficulties related to a change in cognitive status rather than hearing impairment
-the recipient requests additional rehabilitation and training that the audiologist is not able to provide

Hearing Aid Use

If the patient utilizes a hearing aid in the contralateral ear, performance with the hearing aid and the implant will continue to be monitored over time as part of the patient's standard clinical care. Formal evaluation of performance using the hearing aid alone is not included in this study as such monitoring of performance may or may not be performed by the center that is managing the recipient's cochlear implant (ie, a different center may be managing the patient's hearing aid). Testing performed by the implant center will include measures to evaluate performance when using the implant alone as well as when the patient utilizes a hearing aid plus the cochlear implant if the recipient reports that he/she utilizes a hearing aid (either in the ipsilateral or contralateral ear) a minimum of 4 hours each day. These measures include administration of HINT Sentences, CNC Words, and AZ Bio Sentences in the bimodal condition of CI+HA at the 6 and 12 month post-activation intervals.

Six and Twelve Month Test Interval

Audiometric Testing

- Aided soundfield warble tone hearing thresholds at 250, 500, 1000, 2000, 3000, and 4000 Hz
  - CI* alone (note: for all CI alone conditions, the hearing aid is removed from the contralateral ear and the contralateral ear is plugged with a foam plug).

*In all CI conditions, the participant will be instructed to use the speech processor program they use most often in their everyday life.

Speech Perception Testing

- CNC Word Test (Quiet) – one complete list presented at 60 dB(A)
  - CI alone. and
  - CI+HA if patient reports utilizing a a hearing aid in the ipsilateral or contralateral ear at least 4 hours each day*
- AzBio Sentences in Quiet – one complete list presented at 60 dB A
  - CI alone, and
  - CI+HA if patient reports utilizing a hearing aid in the ipsilateral or contralateral ear at least 4 hours each day*

Self-Assessment Questionnaires: Patients will be instructed to complete the questionnaire as it pertains to how they presently hear in everyday listening situations (e.g. when using the CI alone or when using the CI + HA if they use a hearing aid with the CI at least 4 hours each day).

- Health Utility Index (HUI3)
- SF-36 with utility transforms
- APHAB Form A

Hearing Rehabilitation

Traditionally, hearing rehabilitation includes a variety of topics, including orientation to the device, description of strategies to improve hearing in difficult listening situations, utilization of assistive devices and accessories to improve performance, listening and communicating over the telephone, counseling regarding speech recognition outcomes and expectations for performance, and introduction to various home rehabilitation programs such as “Sound and Way Beyond”, the “Listening Room”, and the “Rosetta Stone” to name a few.

Audiologists will be instructed to refer a patient to see a speech-language pathologist for formal hearing rehabilitation services when the patient is not meeting expected levels of performance, when the patient demonstrates difficulty adjusting to the device, when the patient requests additional assistance that the audiologist is not able to provide, or when the patient demonstrates poor open-set recognition with informal assessment. A copy of the informal assessment worksheet that will be used by clinicians to assist with this referral process may be found in Appendix D.

Lastly, clinicians will be encouraged to provide participants with written materials regarding sources for independent rehabilitation and training. Audiologists will complete a checklist at the 6 and 12 month post-activation intervals to indicate they have provided participants with the written materials during a follow up

appointment. A copy of the written materials and the checklist may be found in Appendix D.

Table 1: Summary of data collection visits

		Pre Operative			Post Operative		
	Condition	Candidacy	Baseline	Surgery	Initial Activation	6 Month	12 Month
Informed Consent		X					
Air conduction	Unilateral each ear	X					
Bone conduction	Unilateral each ear	X					
Soundfield audiogram	CI Alone					X	X
	CI Alone						
	Bimodal*						
CNC Words in Quiet	RE aided, LE aided, Bilateral aided		X				
	CI Alone					X	X
	Bimodal*					X	X
AZ Bio Sentences in Quiet	RE aided, LE aided, Bilateral aided		X				
	CI Alone					X	X
	Bimodal*					X	X
Questionnaires							
HUI			X			X	X
SF-36			X			X	X
APHAB Form A			X			X	X
Surgical				X			
Telephone Testing			X				X
Rehabilitation Suggestions					X		

***ADMINISTERED ONLY IF THE RECIPIENT REPORTS HE/SHE UTILIZES A HA IN CONJUNCTION WITH THE CI MORE THAN 4 HOURS EACH DAY**

SAFETY ISSUES

RISKS AND BENEFITS

The pre-specified success criteria for this protocol will be determined based on sentence recognition performance in the best aided condition. Individual levels of margin of effectiveness will be assessed based on post-operative scores on CNC Words and AZ Bio Sentences. A statistically significant improvement in pre- to postoperative performance (six to twelve months postactivation) on scores in the best aided condition based on binomial distribution of Thorton and Raffin, 1978 and the binomial distribution model provided by Spahr et al., 2011.

Risks involved within this study include, but are not limited to, the risks associated with all cochlear implant surgery. It is anticipated that all study participants may permanently lose any residual hearing in the ear to be implanted.

The potential benefits of cochlear implantation include improvement in the participant's ability to understand speech in quiet and in noise, with or without lip-reading, and to better detect speech and other environmental sounds.

SAFETY MONITORING

To monitor device safety (reported through adverse events) throughout the study, medical and audiological observations and procedures are to be reported to the center's Institutional Review Board (IRB) and also to the study coordinating center. Information on all device malfunctions and adverse events will be obtained from the investigational sites and maintained by event type. The surgeon and audiologist will complete a postoperative Adverse Event Questionnaire at each postoperative test interval if any adverse events have taken place (Intraoperative, Initial Activation, 6, and 12 months). The questions in the adverse event form elicit information regarding any surgical, medical, and device-related complications for each study participant.

ADVERSE DEVICE EFFECTS

Adverse device effects refer to any undesirable clinical or medical occurrence associated with use of the device or participation in the study. Any/all adverse device effects are to be reported to the center's IRB and also to the study coordinating center via the Adverse Event Questionnaire. Adverse device effects will be reported if observed, even if they were acknowledged as risk factors in the Informed Consent Form.

UNANTICIPATED ADVERSE DEVICE EFFECTS

Unanticipated adverse device effects refer to any event not identified above that represents a "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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

Investigators are to inform their respective Institutional Review Boards (IRBs) and the study coordinator immediately if an unanticipated adverse device effect is suspected (no more than 10 working days after the investigator learns of the effect). If the case is determined to be an unanticipated adverse device effect, the investigator will fill out an "Unanticipated Adverse Device Effect Form." The study coordinator will report the results of an evaluation of the unanticipated adverse device effect to the FDA and all other reviewing IRBs and investigators within 10 working days after first receiving notice of the event.

STATISTICAL METHODS

STUDY DESIGN

This study is a multi-site, single-arm, repeated-measures design. Each study participant will be evaluated at candidacy and baseline for word and sentence recognition using a variety of tests. Postoperatively, these evaluations will be repeated at 6 and 12 months. To appropriately distribute enrolled study participants across the AZBio score range (41- 60%), we propose two groups (Group A is 41 - 50%; Group B is 51 - 60%). Study participants will be stratified into one of two groups:

- Group A: 45 participants with AZBio (quiet) baseline sentence scores between 41 - 50%
- Group B: 45 participants with AZBio (quiet) baseline sentence scores between 51 - 60%.

STUDY POPULATIONS

Any participant in whom a cochlear implant is attempted to be implanted comprises the intention to treat population (ITT). While technically ITT only applies to randomized trials, the principle of analyzing every participant in whom the device implantation was attempted will be done. The primary effectiveness and safety endpoints will be evaluated with the ITT population. Participants with missing data will have data imputed for these analysis by the methods described in the missing data section.

HYPOTHESIS TESTS AND DATA ANALYSES

Primary Objectives: Efficacy and Safety

Objective 1: Efficacy To evaluate the efficacy of the cochlear implant system under revised cochlear implant indications defined by the widely used clinical test of speech recognition (AZBio sentences presented in quiet). We will evaluate results obtained in patients selected using expanded criteria (41-60% AZBio score at baseline).

For this objective, *efficacy* of the revised cochlear implant indications will be determined using a comparison between *preoperative* scores obtained 1) for the implant ear alone and 2) in the best aided condition, and *postoperative* scores obtained 1) with the cochlear implant alone and 2) in the bimodal (CI+HA) condition if the patient reports he/she utilizes a hearing aid in the contralateral ear a minimum of 4 hours each day. The primary study endpoint, at 12 months post implant activation, will be a statistically significant difference between the mean preoperative and the mean of the two postoperative AZBio sentence

scores. In the adult population, literature suggests that CI effects on speech start to plateau around 6 to 12 months post CI. Therefore, data obtained 12 months post CI will be our primary outcome measure, with an additional assessment at 6 months post CI for two purposes: (1) to assess whether CI effects are linear across 12 months post CI (thus a way to assess the acute benefits of CI); and (2) to provide a more complete post-implant assessment at an earlier date in case the need arises for imputing outcomes at 12 months.

In the primary comparison, the preoperative aided AZBio score obtained with the ear to be implanted will be compared to the postoperative CI alone score. Additionally, the preoperative best aided AZBio score will be compared to the postoperative best aided AZBio score. This best aided AZBio score may include the score obtained when the subject uses CI+HA if he/she has indicated utilization of a hearing aid on the contralateral ear more than 4 hours each day. If the subject does not use a hearing aid in the contralateral ear more than 4 hours each day, the best aided score will be that obtained when using the implant alone.

The primary hypotheses to be tested in the analyses are as follows:

1) that the cochlear implant will significantly improve the AZBio sentence score in the ear to be implanted. The null and alternative hypotheses are given below.

$$H_{01}: \mu_{12} - \mu_0 \leq 30\%$$

versus

$$H_{a1}: \mu_{12} - \mu_0 > 40\%$$

Where μ_{12} is the mean sentence score at 12 months post activation in the implanted ear, μ_0 is the mean sentence score in the ear to be implanted with acoustic only amplification at baseline.

2) that the cochlear implant will significantly improve the AZBio sentence score in the subject's best aided condition. The null and alternative hypotheses are given below.

$$H_{01}: \mu_{12} - \mu_0 \leq 25\%$$

versus

$$H_{a1}: \mu_{12} - \mu_0 > 30\%$$

Where μ_{12} is the mean sentence score at 12 months post activation in the CI+HA condition, and μ_0 is the mean preoperative sentence score in the best aided condition with acoustic only amplification at baseline.

The sentence score is a percentage of the total words tested that were correctly identified by the study participant. Data of this type fit the binomial distribution (Thornton and Raffin, 1978; Spahr et. al, 2011) for each test session, and the data are reported as a percentage. The differences between the pre-implant and 12-month assessment however can be thought of as a continuous random variable. The range of this variable is limited to values between -60 and +59 (given a baseline score restricted to 41-60 for eligibility). If the data on pre-post difference were normally distributed for each test, a paired t-test would be the test of choice. But in this case the distribution of the differences is unknown. The non-parametric analog of the paired t-test is the Wilcoxon signed ranks test. This will be used to test the mean differences from pre-implant to 12 months post-implant in AZBio sentence score recognition at a two-sided alpha of 0.05. A nonparametric test, such as the Wilcoxon Signed-Ranks test will be used to test the null hypothesis for group data because of its increased robustness and high efficiency relative to the t-test. This is the typical approach to examine change in outcome from baseline to a fixed point in time over a specified follow-up period.

To take advantage of having 2 follow-up outcome assessments after CI, we will use mixed effects modeling to examine the progression of sentence score outcome at 6 and 12 months post CI from baseline in a unified approach. This approach follows the intent to treat (ITT) principle and utilize all available data, improves efficiency of statistical inferences by using information afforded by the assessments at 6 months, provides a frame work for likelihood based approach to handle missing data, allows the examination of nonlinear outcome trajectory post implant, and permits studying of effects of subgroups and easy accounting for potential confounds and variables related to missing data.

The basic mixed effects model will include 2 binary indicators in the mean model for follow-up visits at 6- and 12-month, and a full rank, 3x3 unrestricted variance-covariance matrix in the covariance model. The regression coefficient estimates associated with the 2 binary indicators from this model provide estimates of mean outcome change from baseline pre CI to 6- and 12-month post CI, respectively, utilizing all available outcome information from baseline, 6- and 12-month assessments while allowing for different outcome variances at different visits and properly accounting for within subject correlations of these outcomes across visits. The 12-month effect estimates will form the basis for hypothesis testing of the primary outcome, while the 6-month effect estimates could be contrasted to the 12-month estimates to explore for evidence of nonlinear change in outcome trajectory over time following cochlear implantation. All data will be included in the analysis, with missing outcome properly indicated by a statistical software specific missing indicator (e.g., in SAS, a “.”). This modeling approach forms the basis for constructing the likelihood for the observed data in the event of missing data that will provide valid inferences the under missing at random (MAR) mechanism. This approach is equivalent to a properly conducted multiple imputation approach for missing data.

To explore for differential CI effects on sentence score outcome between different patient groups, additional statistical assessments for interaction will be performed. Terms of subgroup indicator by visit can be included in the mean model to characterize the differences in outcome change over time between subgroups. Similarly, potential confounding factors can be easily adjusted for using this modeling approach. Study sites are typically included in this type of analyses to account for potential clustering effects within sites (see below pooling data from study sites for discussion of site by visit interaction). The adjustment could also include variables found to be associated with the occurrence of missing data in outcome to missing data in the observed likelihood--a standard approach frequently employed in data analyses for randomized controlled trials.

Study Variables

An evaluation of the characteristics of the study variables will be done routinely to validate assumptions needed for the statistical test procedures. Histograms will be studied and tests performed to determine consistency of variables with basic assumptions. Our proposed modeling approach does not require the outcome (sentence scores) to be normally distributed. The normality assumption is instead placed upon the model residuals and is frequently satisfied in properly constructed models. Residual analyses will be conducted to ensure validity of statistical inferences under model assumptions. Transformation will be performed when necessary. In addition, a sample size of 90 offers protection based on mean based statistical inferences (through the normal approximation afforded by the central limit theorem).

Data Handling, Missing Data, and Imputation

A. Descriptive tabulation of withdrawn study participants will be provided with the reason for withdrawal. Each study participant will be accounted for. An accountability table will present the total number of study participants, the total number of eligible participants, as well as the total number of evaluable participants by study visit.

B. Missing data from participants who do not have outcomes for the primary endpoints present special problems for analysis when analyzing data from the ITT population, because, to perform an analysis in that population, one needs data on all participants.

All efforts will be put forth to ensure near complete follow-up, with particular focus on the assessment of primary outcomes (as reflected in speech measures at 6 and 12 months) and occurrence of adverse events. Regular reminders of participant follow-up due dates will be provided to participating centers to facilitate scheduling of follow-up visits.

Nevertheless, some missing data will be inevitable. Since all participants will be included in the primary endpoint analysis, any missing scores will have to be properly handled. For data missing under the MAR mechanism, the missing data

will be handled either by appropriate likelihood for the observed data or complete data created through proper multiple imputation. We offer the following consideration for the multiple imputation approach. If the data for the measures 6 months apart are highly correlated (coefficient of 75% or higher) with one or more measurements (prior to or post six months), the method of choice for imputation is regression imputation (Little and Rubin, 2002). A linear regression analysis for the measures among the CC population will be done for the 6-month score and the other value, X_i, to provide an estimate of the slope, b_i, the intercept, a, and the standard deviation (root mean squared error) from the regression $s_{y.x}$. To impute the missing value, a standard normal variate, z, will be chosen at random, and the missing value will be estimated by the following formula:

$$Y = z^*s_{y.x} + a + b_1 X_1 + \ldots + b_k X_k$$

Where k is the number of relevant visits which can range from 1 to the total number of measurements. Since a different seed is used to generate the random selection of the z value, 10 different sets of results will occur for the 10 imputations.

If the correlation is weaker than a correlation of 0.75, then the preferred method of imputation is random selection of participants with an outcome from participants within sub-groups of relevant covariates such that the participants within a sub-group are as alike as possible. Once the sub-groups are formed, within each sub-group, a participant with a missing value is assigned the value of another person within the same sub-group by sampling those participants with values with replacement. Sub-grouping will be done on age (within 10 year groups), gender, duration of hearing loss (overall and severe to profound), and baseline word scores (± 10%). This is done until all participants have been assigned a value for the co-primary endpoints. As indicated above, since a different seed is used to generate the random selection of the participant with a value, 10 different sets of results will occur for the 10 imputations.

In a regression analysis with multiple prior time points, experience indicates that a correlation of 75% provides a reasonably good fit to the dependent variable accounting for at least 56% of the unexplained variation among the endpoints. Noting that the goal of imputation is to choose the method with the lowest variability induced by the imputation, experience has indicated that a regression imputation based on 75% correlation, provides less variability than random selection. Thus a regression with a good fit will have less variability in the imputed estimate that randomly selecting an outcome from patients with assumed like characteristics. Noting that an exact match of characteristics is unlikely, the regression imputation is preferred.

If a participant chooses to withdraw from the study or is lost to follow up, another analytic approach will be taken in generating a conservative model of outcome. These participants will be deemed not missing at random and will be assigned

the lowest score achieved on the test for each outcome variable for the 6-month evaluation.

All multiple imputations will be stochastic imputations to preserve the variability of the imputed value. Also, imputations will be done in a manner that is consistent with the assumptions of multiple imputation theory including missing at random to the extent possible. Comparisons of baseline characteristics of participants with and without missing data will be made to determine if there is evidence of not missing completely at random (MCAR). If the MCAR assumption is clearly violated by the data, observed predictors of missingness will be used in multiple imputation, under an assumption of MAR. Sensitivity analyses will be conducted based on plausible nonmissing at random scenarios (such as assuming loss follow up occurred at the poorest performers).

Imputations will be done 10 times and the results will be combined by method of Rubin (1987) (also discussed in SAS Proc MIANALYZE reference) to obtain an overall p-value for the ten results. The method involves obtaining an overall test statistic based either the imputed distribution of the parameter of interest or the within imputation test statistic. By obtaining an overall mean, and standard error, an overall P-value can be obtained. The standard error of either variable, involves both the within and between imputation variability of the estimates and the test statistic is either a Student's t or normal z variable. The method also provides formulae to compute the number of degrees of freedom for the test statistic in case of a Student's t.

After each imputation, the data will be analyzed as though there was a full data set with the observations resulting from the imputations and will be analyzed as described below.

Analysis of Baseline Characteristics

A. The baseline characteristics of the study group will be presented descriptively. Quantitative variables such as age will be presented with mean, standard deviation, median, minimum and maximum. Qualitative variables such as gender will be presented with number with the condition, the sample size, the percentage, and the 95% two-sided exact binomial confidence intervals.
B. We will explore for the baseline characteristics associated with change in outcomes over time post CI by taking a case-control approach. For example, we will define study groups based on the tertiles (or best improvement, moderate improvement, and no improvement at all) of the12-month change in outcome, and compare the baseline characteristics between these study groups. The analyses will involve comparing mean differences for continuous baseline characteristics (e.g., age, cognitive function score) between groups using ANOVA or it's nonparametric equivalent, and comparing frequency distributions of categorical

baseline characteristics (e.g., surgical technique, cognitive status, implantation devices, implantation strategies) between groups using contingency tables and chi-square tests. These analyses will be repeated based on 6-month outcome changes.

C. Based on exploratory analysis results identified in B. we will include relevant baseline characteristics in our primary analysis models to generate a systematic evaluation of the impact of baseline variables on post CI outcomes. To generate this model, we will include the cross product term of baseline characteristics and visit indicators as interaction terms.

Pooling of Data

Pooling data from study sites is based on clinical criteria given by Meinert (1986): all sites had the same protocol, we monitored the sites to assure protocol compliance, and the data gathering mechanism (case report forms and data acquisition) was the same across all study sites.

Justification of Pooling across Study Sites – The baseline characteristics by study cohort of the study participants will be compared across study sites. Imbalances in baseline characteristics between study sites are not impediments to pooling, but these methods do identify sites or variables that are out of balance. Any imbalance detected in baseline characteristics among study sites identifies that variable as possible covariate in multivariable analyses of safety and/or effectiveness outcomes. One needs to demonstrate that safety and/or effectiveness results are not due to one or more imbalances rather than the device under investigation. There are no statistical impediments to combining data from multiple study sites unless there is a qualitative site by treatment interaction (Steven Piantadosi testimony before the Dispute Resolution Panel, September 6, 2001). This is also the impact of the Meinert reference.

Fleiss (1986) discussed how data should be combined if the outcomes vary by study site to get an overall outcome estimate. We recognize that larger datasets may be needed to evaluate site-specific outcomes. Nonetheless we will attempt to explore the possibility of site-specific patterns of outcome by following recommended procedures. One recommendation is to test for a quantitative site by visit interaction. If it is not significant, the data from the sites can be combined with regard to study site. If the interaction is significant then the outcome from each site should be weighted to get an overall outcome measure from the study. Thus in this trial all data from the study sites will be combined unless there is a qualitative site by treatment interaction (the site exhibiting the interaction will be removed from analysis and special investigation of the site will be done). If the interaction is strictly quantitative, then the outcome from the sites will be a weighted average of the site outcomes with the weight being the inverse of the variance of the site outcome.

Additional Analyses

A. The change from baseline in the word and sentence scores at 6 and 12 months postactivation will be presented descriptively. A descriptive analysis will be provided for all variables, the mean, standard deviation, number tested, median, minimum, and maximum scores.
B. A descriptive analysis of the change from baseline of the Health Utility Index Mark 3 and SF-36 result at 6 and 12 months postactivation will be performed.
C. A descriptive analysis of the change from baseline of the APHAB Form A result to 6 and 12 months postactivation will be performed.
D. A post implant performance review will be conducted once the first 45 subjects enrolled in the study have reached the 6 month post-activation timeframe. The purpose of this review is to detect untoward outcomes early on. The potential patient and clinical factors associated with such post CI outcome deficits at 6 months so that proper considerations could be made regarding modification of patient eligibility and/or adjustment of study procedures for protocol amendment. This review is in addition to routine examinations of patient characteristics in recruited sample to ensure sample representativeness of the target population and standard data monitoring for safety and unforeseen issues..The results of this early performance review will be reported to the CMS in a timely fashion.

STATISTICAL SOFTWARE

The primary analyses will be done using SAS, Version 9.1 or later for Windows. Exact tests of and confidence intervals for qualitative variables will be done with StatXact for Windows Version 8 or later. Some preliminary descriptive analyses and density plots of the data may be done with SYSTAT 10.0.

DATA COORDINATION

Data coordination will be managed by an independent firm named PopsiCube. Their responsibilities will include trial preparation (i.e. development of data collection forms), site monitoring and management, data capture, data management, and statistical analyses. The study's Principal Investigator will oversee the work performed by PopsiCube.

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APPENDIX A

PROCEDURAL CONSIDERATIONS

- All pre and postimplantation testing will be completed using an audiometer, such as a Grason Stadler GSI 61 (Grason Stadler, Inc., Milford, NH, U.S.A.) or equivalent, calibrated to American National Standards Institute (ANSI) standards with maximum output for frequencies of 0.5 to 4 kHz of no less than 120 dB HL.
- Speech recognition and hearing evaluations will be completed in, at a minimum, a single-walled sound booth capable of accommodating a calibrated, 90-degree, speaker orientation.
- Stimuli will be administered using either insert earphones and/or sound field speakers. Applicable ANSI standards are: ANSI/ASA S3.6-2004; ANSI S3.1-1999 (R 2003).
- Pure tone threshold exploration will be completed using the adaptive Hughson & Westlake procedure (1944).
- Sound field calibration will be completed as recommended by Katz (2002). The sound level meter should be set to the “A scale” and “slow” settings. The sound level meter will be placed in the center of sound booth, approximately 1m from the loud speaker face, at the height of which would represent the center of an average participant’s head. The calibration signal (test specific, however preferably speech spectrum noise) will be administered through the audiometer output to the loud speaker within the sound booth. The sound level meter detects the audiometer output through the loud speaker. With the VU meter on the audiometer set to 0, the dial on the audiometer is adjusted until the sound level meter within the sound booth detects the desired output.

APPENDIX B

PRIMARY Outcome Measures

Measure Type: Primary
Measure Title: AZBiosentences test
Measure Description: A list of recorded sentences presented to subjects prior to receiving a cochlear implant while they use hearing aids. Subjects repeat each word of the sentence that they can understand and are given a percent correct score based on the percentage of words correctly understood. The test is administered again after receiving a cochlear implant to determine if their ability to recognize words in sentences has improved.
Time Frame: Prior to receiving a cochlear implant and 6 and 12 months post-cochlear implant.
We hypothesize that CI effects will be substantial if not peaked at 6M after activation. Therefore we will have a comprehensive outcome assessment 6M post CI. To affirm this outcome post CI, we will repeat a comprehensive outcome assessment at 12M post CI, which will allow us to identify whether a nonlinear growth curve exists. With 2 post CI assessments, we will also have better information on which to perform missing data imputation (under the missing at random mechanism should imputation become necessary).
Safety issue? No

SECONDARY Outcome Measures

Measure Type: Secondary
Measure Title: CNC Word Test
Measure Description: Similar to the HINT sentences test, but instead a list of recorded one-syllable words are presented. The test is administered prior to and after receiving a cochlear implant to determine if their ability to recognize one syllable words has improved.
Time Frame: Prior to receiving a cochlear implant and 6 and 12 months post-cochlear implant.
Safety issue? No

Measure Type: Secondary
Measure Title: Health Utility Index Mark 3 (HUI3) Questionnaire

Measure Description: The HUI is a family of generic health profiles and preference-based systems that measure health status and health-related quality of life.
Time Frame: Prior to receiving a cochlear implant and 6 and 12 months post-cochlear implant.
Safety issue? No

Measure Type: Secondary
Measure Title: SF-36 with utility transforms
Measure Description: This is a multi-purpose short-form health survey that provides an 8 scale profile of functional health and wellbeing as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index using utility transforms.
Time Frame: 6 months, 12 months
Safety issue? No

Measure Type: Secondary
Measure Title: Resource Use and Expenditure Questionnaire
Measure Description: This instrument focuses on costs associated with hearing loss. The questionnaire will be administered prior to and after the subject receives a cochlear implant and will aid in providing information relative to the cost of effectiveness of cochlear implants
Time Frame: Prior to receiving a cochlear implant and 6 and 12 months post-cochlear implant.
Safety issue? No

Measure Type: Secondary
Measure Title: Abbreviated Profile of Hearing Aid Benefit (APHAB)
Measure Description: This is a 24 item self-assessment questionnaire scored in four subscales: Ease of Communication, Reverberation, Background Noise, and Aversiveness to Sounds.
Time Frame: Prior to receiving a cochlear implant and 6 and 12 months post-cochlear implant. ,.
Safety issue? No

OTHER PRE-SPECIFIED OUTCOME MEASURES
None