An Early Feasibility Study of the Safety and Efficacy of the Nucleus 24 Auditory Brainstem Implant in Children with Cochlear or Cochlear Nerve Disorders Not Resulting from Neurofibromatosis type II

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Study Objective

The purpose of this feasibility study is to demonstrate the safety and efficacy of the Nucleus 24 Multichannel Auditory Brainstem Implant (ABI, Cochlear Corp, Sydney, AUS) in children who do not have the diagnosis of neurofibromatosis type II (NFII), and who have either experienced failed cochlear implantation (CI) or have been unable to receive a CI secondary to cochlear or cochlear nerve disorders. These conditions can include: developmental or acquired cochlear nerve deficiency (CND), cochlear aplasia (Michel), post-meningitis cochlear ossification, or cochlear malformation. This study proposes to implant up to 10 pre-linguistic young children (18 mos to 5 yrs. of age) and 5 post-linguistic children (<18 yrs of age) with the Nucleus 24 Multichannel ABI in an attempt to demonstrate safety of the surgical procedure, tolerance of device stimulation, and the potential for auditory benefit beyond that experienced with their CI. This study will provide the preliminary experience for a larger scale clinical trial.

Regulatory Status of the Investigational Device

Data supporting the safety and effectiveness of the Nucleus 24 ABI were provided to the United States Food and Drug Administration (FDA) in March 2000, as part of a Premarket Approval Application. On July 21, 2000, the Agency's Ear, Nose and Throat (ENT) Advisory Panel unanimously recommended that FDA release the Nucleus 24 ABI for use by individuals with NFII above the age of 11 years. Cochlear Americas received a letter of approval from the Agency in October 2000 (PMA No P000015). The letter is enclosed.

The Nucleus 24 ABI features a multichannel electrode lead that terminates in twenty-one, 0.7 mm platinum disk-electrodes. The 21 platinum contacts are arranged on the surface of a silicone rubber pad in three rows of seven contacts and are surgically placed on the surface of the brainstem; specifically, on the surface of the cochlear nucleus.

Background and Rationale

According to Stone, "Hearing impairment strikes at the very essence of being human, because it hinders communication with others" (1). Children born deaf (i.e. pre-linguistic deafness) have severe delays in speech and language acquisition that can retard their social and emotional development, influencing educational and career attainment (2). The pre-linguistic deafened child seldom develops significant understandable speech, and is often socially stigmatized by those in the hearing world (3). Thus, individuals with untreated congenital deafness are often integrated into a separate "deaf community." Hearing impairment negatively impacts upon educational attainment, employment opportunities, income, healthcare utilization, and life expectancy (1, 4-15). As most deaf children are educated outside of the mainstream setting and ultimately achieve lesser levels of employment and income, lifetime losses for having untreated severe to profound hearing loss have been estimated at over $1 million dollars per child ($297,000 added expenditures) (16-18). By comparison, these lifetime costs are significantly higher than for near drowning ($98,500), accidents from firearms ($89,100), stroke ($129,200), rheumatoid arthritis ($130,500), and epilepsy ($172,900), and are similar to those for the devastating illness of schizophrenia ($295,000). In addition to cost, deafness also contributes to an increased risk for depression, anxiety, and physical dysfunction (7, 8 19-21). In summary, untreated deafness is a major disability that negatively impacts upon all aspect of life.

A CI is an auditory, neural stimulating prosthesis. These devices use a multiple electrode array that is inserted into the cochlea to electrically stimulate the auditory (i.e. cochlear) nerve in cases of severe to profound hearing loss. Using specialized speech processing and encoding strategies, these devices can restore sound awareness and significantly improve speech perception in both quiet and noise. Improved speech perception restores communication for adults and allows children to develop spoken language (22, 23). Thus, CIs alleviate many of the disabling effects of deafness described above. In addition to quality of life benefits, the cost-utility of this intervention is positive for both adults and children (24, 25).

The only absolute contraindication to CI is an absent cochlea or an absent cochlear nerve. In addition, patients at risk for lower levels of performance include those with anatomic conditions that adversely affect the electrode-neural interface such as developmental labyrinthine malformations and cochlear ossification and fibrosis secondary to meningitis. While the diagnosis of cochlear (i.e. Michel) aplasia is clear clinically, the diagnosis of cochlear nerve aplasia is made somewhat more challenging by the spatial resolution of current imaging modalities (26-29). Because of this uncertainty, the term cochlear nerve deficiency (CND) was coined to refer to the situation where the cochlear nerve is small or absent on high resolution magnetic resonance imaging (MRI), or where the bony cochlear nerve aperture and canal are small or absent on temporal bone computed tomography (CT). The clinical diagnosis of CND includes these imaging findings in the setting of profound hearing loss (29, 30). Auditory brainstem response testing that shows a present cochlear microphonic but absent neural waves can support the diagnosis (29).

In an effort to provide hearing to deaf children who have inner ear malformations, CND, or ossification from meningitis, CI has been undertaken over the years (30). This might be considered the standard of care today for those who desire spoken language communication. Results of these interventions suggest that most children with CND gain some sound awareness from these devices using higher levels of electrical stimulation. However, achievement of open set speech perception for the purposes of speech and language development has been largely unsuccessful, probably as a result of a poor electrode-neural interface and other associated conditions (30-33). In the study from our institution, only 19% of children with CND developed any open set speech perception using their CI, and none of these children were able to communicate using auditory-only information (i.e. all used some supplemental sign language).

The ABI is an electronic device designed to convert environmental sounds into electrical impulses that are delivered along a multiple electrode array situated in close proximity to the cochlear nucleus in the brainstem. In a manner similar to the cochlear nerve, the cochlear nucleus maintains some degree of tonotopic arrangement; thus, application of discrete electrical stimulation along certain spatial locations within the lateral recess of the 4th ventricle results in discriminable psychophysical frequency percepts (i.e. pitch). The ABI is indicated for patients where the cochlear nerve is absent or unavailable for stimulation bilaterally. Most commonly, adults and children with hearing loss secondary to NFII with bilateral acoustic (8th nerve) tumors have been the main group of patients implanted to date.

In general, outcomes from ABI can be described in terms of sound detection and speech perception abilities using closed- and open-set test materials with and without the addition of lip-

reading. In a recent review of 86 NFII patients implanted with ABIs, 13 did not respond to stimulation and 1 was explanted (34). Of the 60 patients with available 6-month data, mean open-set speech perception scores (CUNY sentences) using the implant alone, vision alone, and both the implant and vision on CUNY sentence were <10%, 30%, and nearly 55% correct. However, there was a wide range of auditory abilities, with some patients obtaining combined vision and sound scores of >90% correct (34). Thus, in patients with NFII, the ABI is an excellent enhancement to lip-reading. For individuals that have known only spoken language throughout their entire life, this connection to the speaking world is significant, and the importance of this communication enhancement should not be underestimated.

Experience with Auditory Brainstem Implantation in Patients without NFII

The effectiveness of ABI for patients without NFII has only recently been explored (35-43). Colletti et al. in Verona, Italy, have summarized their results of a group of *adult patients* with a variety of conditions (excluding NFII) that received an ABI between 1997 and 2007 (40). Results were compared to a group of 34 individuals with NFII implanted by the same surgeon. The duration of deafness ranged from 3.2 to 8.5 years (X = 5.1; SD = 2.4) for the NFII group and ranged from 1.2 to 19.8 years (X = 9.6; SD = 5.9) for non-NFII group. All non-NFII patients were implanted through a retrosigmoid craniotomy. NFII patients also required tumor removal prior to placement of the ABI.

After at least one year of device use, using audition alone, sentence recognition ranged from 10 to 100% (X = 59%; Median = 53%; SD = 21.34) in the non-NFII group (n = 48) and from 5 to 31% (X = 10%; Median = 16%; SD = 15.21) in the NFII group (n = 32). These values were significantly better (p = 0.0007) in the non-NFII subgroup. Table 1 below, adapted from Colletti et al (2009), shows the sentence recognition score (type not specified) outcomes for the various etiologies without NFII (40). Except for those adults with auditory neuropathy, sentence recognition scores in these adult patients are significantly better than in the patients with NFII.

TABLE 1. Open-set sentence recognition 1-10 yrs. after ABI.

Cause	No. Subjects	Range,	% X	SD	T versus NT	t test
Head trauma	7	32-80	62	57	23,41	p = 0.005
Auditory neuropathy	4	12-18	15	16	2,52	p = 0.07
Cochlear malformations	6	37-61	44	61	11,2	p = 0.006
Altered cochlear patency	31	34-100	60	64	19,81	p = 0.0048

x-mean; Med-median, sd-standard deviation, T-tumor (NFII), NT-non-tumor

Based on these results, the investigators concluded that adults with acquired conditions that are isolated to the cochlea or cochlear nerve such as otosclerosis (altered cochlear patency) and traumatic cochlear nerve avulsion are better candidates for ABI success than those individuals with NFII. They hypothesized that NFII and/or its treatment results in pathological changes in the brainstem and cochlear nuclei that might preclude good performance with an ABI. Similarly, congenital malformations and auditory neuropathy might produce central nervous system changes that are not conducive to the development of open set speech perception using an ABI, possibly as a consequence of long-term auditory deprivation.

In theory, children would be better candidates than adults for an ABI since they have substantial developmental plasticity and have no auditory memory that requires precise matching

of signals. Colletti and colleagues in Verona, Italy, have placed *ABIs in children* without NFII and have summarized their experience in 2008 (41). In that study, 26 children (17 in Verona; 9 in other countries) aged 14 months to 16 years received an ABI for different tumor and non-tumor diseases between 1996 and 2006. Etiologies included cochlear nerve aplasia with or without associated inner ear malformations (n=19), NFII (n=2), incomplete cochlear partition (n=2), auditory neuropathy (n=1), post-meningitis ossification (n=1), and temporal bone fracture with nerve avulsion (n=1). Fourteen children had a variety of other disabilities including: mild motor delay (n=8), learning disability (n=7), behavioral impairment (n=7), cognitive delay (n=8), language delay (n=6), and 2 with visual impairment. Six children received previous CIs with no auditory results. All were operated through a retrosigmoid craniotomy, and there was one reported major complication (detailed below). Results showed that all children consistently use their devices (avg. 8 hrs./day) and demonstrated gradual improvement in communication skills, showing more attention and interest in school and at home. From an auditory perspective, 20 pre-linguistic and 4 post-linguistic children have environmental sound awareness, detection of instrumental sounds and lip-reading enhancement; 3 pre-linguistic and 2 post-linguistic children achieved bi-syllabic word recognition as well as understanding of simple commands, but only one post-linguistic child had open set recognition (average 50% correct responses) and can perform the speech tracking test. Cognitive testing in a subset of 9 children using the ABI demonstrated improved selective visual-spatial attention (form completion subtest) and fluid (multisensory) reasoning (repeated patterns subtest) when compared to a group of 4 congenitally deaf children without an auditory assistive device.

Sennaroglu et al. implanted 6 children with severe inner ear malformations using the Nucleus 24 ABI. These children gained basic auditory function and were able to recognize and discriminate sounds such as the doorbell and telephone by the third month of usage. Two children had developed open set discrimination scores at that time (42). As of 2011, 21 children had received the same ABI for inner ear malformations in the same implant center in Turkey. No child has been unresponsive to implantation, and the number of active electrodes ranges from 8 to 20. Five children are reported to have variable degrees of open set speech perception (no details). When the pre- and post-operative linguistic gap (receptive and expressive) are compared, the majority had either decreased or stabilized the gap suggesting that ABI is effective in the language development of these children. Almost all children where the gap still increased in spite of ABI had additional handicaps. It was concluded that the presence of additional handicaps is the most important limiting factor in the language development of ABI in children with severe malformations (43).

A child implanted in Verona was seen at the University of North Carolina at Chapel Hill (UNC) in 12/2009 for evaluation. He was implanted at 3 yrs. of age for CND with the Nucleus 24 Multichannel ABI through a retrosigmoid approach. His MRI and CT confirmed the anatomic findings and audiometric testing without his device revealed a profound hearing loss. After nearly 4 years of implant use (7 yrs. of age), the child scored 100% on an ESP-monosyllabic word test (12-choice, closed set pictures) and 81% and 48% on PBK phoneme and word scores (open set *without* visual cues), respectively. Evaluation by our team speech pathologist revealed that the child was a functional spoken language user in that he was able to produce complex sentence structure, although he did have some articulation errors that appeared to be related to oral-motor deficiencies. He could actively argue with his older brother in the exam room using oral language alone.

In summary, the ABI appears to provide auditory awareness in all children. Emerging data suggest that some children without significant associated handicaps are beginning to develop open set speech perception and oral language. While further study is clearly needed, this approach appears promising for the limited subset of deaf children who cannot benefit from a CI.

Complications from Auditory Brainstem Implantation

Complications related directly to the ABI have been unusual. Toh and Luxford indicated the most common complications in ABI surgery appear to be cerebrospinal fluid (CSF) leak, electrode migration, and non-auditory side effects during stimulation (44). Fatal complications are exceedingly rare. Laszig et al. reported one NFII patient that died following tumor removal and ABI insertion as a result of pulmonary embolism and pneumonia (45). Grayelli et al. also reported one fatal embolism (46). These complications were more likely related to extended duration posterior fossa surgery rather than ABI surgery, specifically. Electrode migration appears to be a complication that occurs in patients undergoing ABI in the setting of tumor removal where distorted brainstem anatomy results in a shallow or deformed lateral recess. Following surgery, brain re-expansion might displace the electrode.

CSF leaks are an expected risk from any surgery where CSF is encountered. Otto et al reported 2 CSF leaks among 61 patients following translabyrinthine tumor removal and ABI placement that resolved with either a pressure dressing or a temporary lumbar subarachnoid drain (47). Grayelli et al. also reported 2 cases of CSF leaks after 31 ABI surgeries, and Sennaroglu et al. reported one case of a CSF leak in a child who underwent retrosigmoid ABI placement that resolved with wound exploration and repair of the air cell opening (42, 43).

Colletti et al reported on 114 ABI operations performed through the retrosigmoid approach in Verona from 1997 to 2008 in 83 adults and 31 children (48). Thirty-six had NFII (34 adults and 2 children), and 78 (49 adults and 29 children) had cochlear or cochlear nerve disorders unrelated to NFII. Table 2 below details the complications from this study. There was a statistically lower risk for complications among the patients without NFII, presumably because there was no need for tumor removal prior to device placement. Importantly, there was 1 major complication in a child implanted in Manchester, England. That child developed a cerebellar contusion and swelling requiring a return to the operating room for clot evacuation. This child recovered without neurological sequelae.

Other complications in children included wound seroma (n=4) that were managed with aspiration and bandage, minor wound erythema treated with antibiotics alone, and transient balance problems that resolved without treatment.

Non-auditory side effects are a relatively common occurrence from ABI stimulation and are usually related to activation of the neural tissue in the region of the implant. Toh and Luxford reported non-auditory side effects in 42% of multichannel ABI users (44). Colletti et al (48) reported that ipsilateral body tingle was observed in 2 children (6.9%), facial nerve stimulation in 2 (6.9 %), dizziness in 1 (3.4%), headache in 1 (3.4%), and throat tingle/tickle in 1 (3.4%) child. In adults, ipsilateral body tingle was observed in 10 subjects (8.7%: 7 NFII and 3 non-tumor), facial nerve stimulation in 6 (5.2%: 4 NFII and 2 non-tumor), dizziness in 15 (19%: 9 NFII and 6

non-tumor), headache in 5 (6 %: 3 NFII and 2 non-tumor), and throat tingle/tickle in 8 (9.6%: 5 NFII and 3 non-tumor). These side effects are all alleviated with selective electrode deactivation. Re-activation of the offending electrode over time usually resolved the issue.

TABLE 2. Complications in ABI patients.

	NFII	Non-tumor	
	Ad	Ad	Ch
Major complications			
Mortality (unrelated to ABI)	3	0	0
Cerebellar contusion	1	0	1
Permanent facial palsy	1	0	0
Meningitis	1	2a	1a
Lower cranial neuropathy	2	0	0
Hydrocephalus	1	1	0
Pseudomeningocele	2	0	0
Cerebrospinal fluid leakage	6	1	0
Minor complications			
Transient hydrocephalus	7	1	0
Wound seroma	4	2	4
Minor infections	2	2	1
Balance problems	11	2	1
Infection around implant	2	2	0
Infection surgical flap	2	1	0
Transient facial palsy	8	0	0
Temporary dysphonia and difficulty in swallowing	0	0	1
Headache	8	3	0
Flap problems	2	0	0
Non-auditory side effects	28	16	7

(a) Approximately 2 years after ABI activation.
Ad, adults; Ch, children.

Benefits and Risks

The benefits and risks of ABI in children are listed in TABLE 3 based on a compilation of previous literature using the ABI in the proposed population, personal experience with posterior fossa surgery at UNC and in the literature, and the experience of children that have received cochlear implants for severe to profound hearing loss. The sections above detail the outcomes from the medical literature and the individual benefits and risks as well as others not previously mentioned are in the table below.

TABLE 3. Potential Benefits and Risks of ABI

Potential Benefits	Potential Risks

• Hearing:
  ○ Sound awareness
  ○ Speech perception
  ▪ Sound awareness
  ▪ Closed-set
  ▪ Open-set
  ○ Music appreciation
• Speech and Language Acquisition
• Enhanced Communication
  ○ Oral
  ○ Improved lip-reading
  ○ Total
• Educational Achievement
• Employment Opportunities
• Quality of Life
• Reduced Costs secondary to:
  ○ Mainstream Education
  ○ Meaningful Employment
	• Vascular injury with
	  ○ Bleeding,
	  ▪ Epidural hematoma
	  ▪ Subdural hematoma
	  ▪ Subarachnoid hemorrhage
	  ▪ Brain contusion,
	  ○ Thrombosis
	  ▪ Ischemic stroke
	• Infection
	  ○ Wound
	  ○ Central nervous system
	  ▪ Meningitis
	  ▪ Cerebritis/Encephalitis
	  ▪ Epidural Abscess
	  ▪ Subdural empyema
	  ▪ Brain abscess
	  ○ Device
	• Cranial nerve injury
	  ○ Trigeminal nerve-facial numbness or pain
	  ○ Facial nerve-paresis or paralysis
	  ○ Cochlear nerve-hearing loss
	  ○ Vestibular nerve-vertigo or imbalance
	  ○ Glossopharyngeal/Vagus nerves-vocal fold paresis or paralysis, palatal paresis or paralysis, with resulting dysphagia, aspiration hoarseness
	  ○ Spinal accessory nerve-shoulder dysfunction and winged scapula
	  ○ Hypoglossal nerve-tongue deviation, dysarthria, and dysphagia
	• Cerebrospinal fluid disorder
	  ○ Leakage (wound or rhinorrhea)
	  ○ Pseudomeningocele formation
	  ○ Hydrocephalus
	• Death
	
	• Non-auditory stimulation from the device
	  ○ Facial pain or twitching
	  ○ Throat tickle, spasm, or pain
	  ○ Shoulder twitching
	  ○ Hemibody tingle
	
	• Device Failure

Potential Benefits (see **"Experience with Auditory Brainstem Implantation in Patients without NFII"** for literature review).

Children receiving the ABI in the present study have a very realistic chance for gaining improved sound awareness, enhanced lip reading, and limited closed set speech (pattern perception) understanding with the device. This has been previously demonstrated for both adults (>18 yrs of age) with and without NF2 as well as for children (<18 yrs) without NF2. In most instances, this will represent a significant improvement over that obtained using their CI. Higher levels of closed set (words) and open set speech understanding have been demonstrated in some adults and children using the ABI. As age of implantation and the presence of developmental and cognitive delays negatively impact upon a child's ability to achieve this level of performance, the chances of this outcome for children in the present study remain unknown since most of those implanted in other parts of the world had these complicating, negative prognostic factors. This study will actively control for these variables by only implanting younger (18 mo to 5 yrs) pre-linguisitc children without such delays or those that are post-linguistic (< 18 yrs with previous open-set speech perception using a cochlear implant). Our group at UNC as well as others has personally tested children that have obtained significant open-set speech perception abilities using the ABI alone (implanted in Italy). As in CI, increased speech perception abilities can improve speech and language acquisition, educational achievement, employment opportunities and quality of life. These long-range benefits very much depend on the speech perception abilities of the child using the ABI device. If the device fails to provide sound awareness or improved speech understanding, then the remaining benefits are much less likely.

Potential Risks (see "**Complications from Auditory Brainstem Implantation" for a literature review)**

Risks and complications from ABI surgery are expected to be uncommon but can potentially be serious. Majors complications such as bleeding in or around the brain including major cerebellar contusion should be very unlikely since extensive dissection, such as is undertaken in tumor surgery, will be unnecessary. In tumor surgery, the risk of major bleeding is well below 2%. At UNC, we have had one major posterior fossa hemorrhage in our last 164 acoustic tumor cases (0.6%). In a large series (n=4400) from the literature of non-tumor posterior fossa craniotomies performed for microvascular decompression, the risk of cerebellar injury (parenchymal bleeding/contusion) was less the 1% and major other hemorrhage was much less common. Thus, the risk for intracranial hemorrhage and/or cerebellar injury with subsequent stroke is small. CSF leakage from the wound or from the nose (rhinorrhea) can also occur. This will likely be the most common surgical complication. Given the lack of need for internal auditory canal drilling (as in acoustic neuroma surgery); the leak risk will be well below 10% (that seen for acoustic neuroma surgery in the literature). At UNC, our leak rate was <8% (n=13) for our last 164 acoustic tumor cases. In the microvascular decompression literature, the CSF leak rate is <2%. The etiology of rhinorrhea, should it occur, will also be very clear since internal auditory canal drilling is not required in this surgery. Rhinorrhea will arise from exposed mastoid air cells in the cranial opening. Similarly, the risk of cranial nerve injury will be unlikely since the anatomy will not be obscured by pathology such as tumors or infection. While cranial nerve 8 and 9 border the lateral recess of the 4th ventricle (Foramen of Luschka), neural dissection will likely be mostly unnecessary and not obscured by tumor. Infection risk can include meningitis. This risk is less than 2% as a complication from craniotomy in the literature. The risk of device loss from infection is also very small.

Non-auditory stimulation is expected to occur in roughly 20% of subject. Symptoms can include: facial pain or twitching, throat tickle, spasm, or pain, shoulder twitching, and hemibody tingle. Altering electrode maps and activation patterns can minimize or eliminate such stimulation. While not likely, there is the remote potential for large numbers of electrodes to require deactivation to the point that auditory stimulation will not be effective. Also, while not reported in this population, the theoretical possibility for cardiac arrest from stimulation along the lower cranial nerves.

When balancing the benefits and risk of ABI surgery in children, there is no truly comparable surgical cohort for the population in question. However, when one considers microvascular decompression surgery for disorders such as trigeminal neuralgia and hemifacial spasm, the risks of ABI surgery are expectedly similar (and very low) and the potential benefits for the deaf child undergoing ABI far exceeds those benefits enjoyed by the vascular compression population. While facial pain and twitching are problematic for those with vascular compressive disorders, the impact of life-long deafness on a child are profound. As previously pointed out, children born deaf (i.e. pre-linguistic deafness) have severe delays in speech and language acquisition that can retard their social and emotional development, influencing educational and career attainment (2). The pre-linguistic deafened child seldom develops significant understandable speech, and is often socially stigmatized by those in the hearing world (3). Thus, individuals with untreated congenital deafness are often integrated into a separate "deaf community." Hearing impairment negatively impacts upon educational attainment, employment opportunities, income, healthcare utilization, and life expectancy (1, 4-15). As most deaf children are educated outside of the mainstream setting and ultimately achieve lesser levels of employment and income, lifetime losses for having untreated severe to profound hearing loss have been estimated at over $1 million dollars per child ($297,000 added expenditures) (16-18).

Protocol

This study is an early feasibility study of the Nucleus 24 ABI in children without NFII. It will be conducted as a repeated-measures, single subject experiment with up to 10 replications (i.e. 10 total subjects). A single-subject research design was chosen (in which each subject serves as their own control) in order to accommodate the heterogeneity that is well known to characterize auditory prosthesis research. Post-operative evaluations will be conducted at the initial activation and at 1, 3, 6, 12, 18, 24, 30, and 36-month intervals post-activation. A 36-month follow-up was chosen in an effort to demonstrate the emergence of open-set speech perception abilities prior to study cessation. Experience in the CI literature has shown that a minimum of 2 years of device usage is required for children with pre-lingual hearing impairment to develop some open-set speech perception abilities (50). Blinding or masking procedures are not included in the design, as the presence/absence of a brainstem implant cannot be easily concealed from the device recipients and/or clinical investigators.

Preoperative measures will include high-resolution brain MRI, temporal bone CT and standardized, developmentally appropriate audiological and speech and language development test batteries. Children between 18 mo and 5 yrs of age with one of the anatomic conditions mentioned below and a present and patent cochlea will have previously received a CI as a precondition prior to consideration and will have demonstrated very limited to no benefit from

the device based on a lack of development of significant closed set (more than pattern perception) or open set speech perception, and failure to achieve developmentally appropriate language growth during the follow up period. Those without a present or patent cochlea will be implanted with the ABI without the need for previous CI. Post-linguistic children (<18 yrs) will have had a CI but lost or lacked benefit from an appropriate CI and have no potential for revision CI surgery to improve their condition. The side/ear contralateral to the previous placed CI will be chosen, unless not possible (eg. bilateral CIs), to avoid potentially same-side, unwanted surgical and processor interactions as well as to allow comparison of performance in the follow-up period. If ABI needs to be considered ipsilateral to the previous CI, removal of the CI will need to be considered. Surgical interaction would be the issue of needing to operate in and around the CI device putting it at risk of damage. Unwanted processor interactions would be problematic if the receiver stimulator of the previous CI and the ABI were located in the same region. The ABI processor headpiece might be attracted to the CI receiver stimulator.

Following implantation of the investigational device and at least 4-6 weeks of healing, the ABI will be activated in a controlled setting and auditory performance assessed at the previously proposed intervals (1, 3, 6, 12, 18, 24, 30, 36 months). Subjects will be evaluated using the Nucleus Speech Processor and programmed with an approved sound processing strategy. Post-operative auditory function will be evaluated using behavioral audiometry and commonly used, developmentally appropriate measures of speech perception, speech production and language. Auditory function will also be assessed using electrophysiological tests at appropriate intervals.

SPECIFIC AIMS

Aim 1: Demonstrate the safety of ABI surgery in children.

Aim 2: Demonstrate the development of sound awareness and improved speech understanding among children implanted with the ABI when compared to their baseline skills.

Aim 3: Demonstrate the development of oral language skills following the use of the ABI that were not evident prior to its use.

Methods and Subjects

Up to 10 subjects will be enrolled in the study at the sponsoring location. Qualified subjects must meet the following inclusion criteria and must not exhibit any of the exclusion criteria.

Inclusion Criteria

- Pre-linguistic hearing loss (birth-5 yrs.; age at ABI 18 months-5yrs) with both:
    - MRI +/- CT evidence of one of the following:
        - Cochlear nerve deficiency
        - Cochlear aplasia or severe hypoplasia
        - Severe inner ear malformation
        - Post-meningitis ossification
    - When a cochlea is present or patent, lack of significant benefit from CI despite consistent use (≥6 mo.)
        - No or limited speech perception ability (limited to pattern perception on closed set testing materials using the CI)

- Lack of progress in auditory skills development

18 months of age was chosen for the lower age limit to minimize the adverse effects of auditory deprivation on speech perception, speech production, and language development (23, 50). Moreover, 18 months of age will allow for a child to receive a CI at 1 year of age and have at least 6 months of device experience prior to considering ABI. Six months of CI usage prior to ABI consideration was chosen as this time period to allow for clear demonstration of lack of benefit as defined as either: (1) lack of sound awareness, or (2) where elevated charge requirements, absent ECAPs, elevated pure tone averages (>45 dB), and no or limited speech perception abilities are evident. To determine if a child is making significant progress both subjective and objective measures are used. Objectively, standardized speech perception, production, and language tests (as described below) are administered to determine if standard scores are following typical developmental patterns, even at a reduced rate. No or limited speech perception abilities will be considered when there are no improvement in IT-MAIS, or ESP measures from preop measures at the 6 month post-CI interval (30, 50). Developmental norms are also determined based on the hearing age. For example, a child who is 9 months old receptively understands between 3 and 50 vocabulary words and approximately 300 between the ages of 2 and 3. Does the child with a hearing age of 9 months understand this many words? For early speech development, all English vowels should be present by a hearing age of 12 months. Children 18 months of age can be tested using the standardized measures to determine progress.

From a surgical perspective, 18 months of age is a sufficient size and weight in most instances to consider ABI surgery. Factors that increase the anesthetic risk (particularly cardiac arrest) among children undergoing surgery include: age<1 yr, obesity, other associated co-morbidities, ASA-PS ≥3, emergency surgery. Moreover, children undergoing elective surgery should be free of upper respiratory tract infection to reduce the risk of respiratory tract complication. Importantly, it is currently standard practice to undertake CI between 1 and 2 years of age. The risk for anesthetic-related complications will be no different for this proposed group of children undergoing ABI surgery (58). While not specifically studied, the risk of major blood loss from ABI surgery is relatively small since tumor resection is not needed. If Chiari posterior fossa decompression surgery among children serves as a surrogate for blood loss risk in this population, a recent meta-analysis suggested only 1 of 246 children experienced any bleeding related complication from this type of surgery (59). As stated below, children with any medical co-morbidities that place them at an increased risk for complication will be avoided in this trial.

- Post-linguistic hearing loss (<18 yrs. of age) with both:
    - Loss or lack of benefit from appropriate CI without the possibility for revision or contralateral implantation. Examples might include:
        - Post-meningitis ossification
        - Bilateral temporal bone fractures with cochlear nerve avulsion
        - Failed revision CI without benefit
    - Previously developed open set speech perception and auditory-oral language skills
- No medical contraindications
- Willing to receive the appropriate meningitis vaccinations
- No or limited cognitive/developmental delays which would be expected to interfere with the child's ability to cooperate in testing and/or programming of the device, in

developing speech and oral language, or which would make an implant and subsequent emphasis on aural/oral communication not in the child's best interest
- Strong family support including language proficiency of the parent(s) in the child's primary mode of communication as well as written and spoken English.
- Reasonable expectations from parents including a thorough understanding:
    - of potential benefits and limitations of ABI
    - of parental role in rehabilitation
    - that the child may not develop spoken language as a primary communication mode or even sufficient spoken language to make significant academic progress in an aural/oral environment
- Involvement in an educational program that emphasizes development of auditory skills with or without the use of supplementary visual communication.
- Able to comply with study requirements including travel to investigation sites.
- Informed consent for the procedure from the child's parents/legal guardian.

Exclusion Criteria

- Pre- or post-linguistic child currently making significant progress with CI

This will be considered if a child is progressing along the expected speech reception hierarchy (SRI-Q) as detailed by Wang et al (50). Even for the very young children (18 months of age with 6 months of use), nearly all children with a good auditory signal from their CI will have reached ceiling effects on the IT-MAIS and have pattern perception beyond chance using the ESP (50). Moreover, there will evidence of improvement in these metrics over time.

- MRI evidence of one of the following:
    - normal cochlea and cochlear nerves or NFII
    - brainstem or cortical anomaly that makes implantation unfeasible
- Clear surgical reason for poor CI performance that can be remediated with revision CI or contralateral surgery rather than ABI.
- Intractable seizures or progressive, deteriorating neurological disorder
- Unable to participate in behavioral testing and mapping with their CI. If this appears to be an age effect, ABI will be delayed until we can be assured that the child will be able to participate, as reliable objective measures of mapping are currently not available for mapping these devices.
- Lack of potential for spoken language development. This will be considered the case when evidence of the following exist:
    - Severe psychomotor retardation, autism, cerebral palsy, or developmental delays beyond speech that would preclude usage of the device and oral educational development. Autism is a special case where there is the potential for delayed presentation. When early signs are considered present, our group routinely requests a comprehensive developmental assessment for further evaluation prior to considering routine evaluation. A specialized group is readily available at our institution for such an evaluation.
- Unable to tolerate general anesthesia (cardiac, pulmonary, bleeding diathesis, etc.).
- Need for brainstem irradiation
- Unrealistic expectations on the part of the subject/family regarding the possible

benefits, risks and limitations that are inherent to the procedure and prosthetic device.
- Unwilling to sign the informed consent.
- Unwilling to make necessary follow-up appointments.

Device

Subjects will be implanted with the commercially available Nucleus 24 Multichannel ABI and fitted with an approved Nucleus speech processor (Cochlear Corp, Sydney, AUS).

Procedures

All subjects will have the following study visits: Pre-operative visit(s), surgical implantation and hospitalization, post-operative follow-up, initial activation (4-6 weeks post-implantation), 1, 3, 6, 12 18, 24, 30, 36 month visits. The following procedures will be carried out at the appropriate interval visits.

Study Protocol Procedures Overview

	Screening	Enrollment	Preop	OR	Day 1	Day 2-5	Initial Stimulation	Month 1	Month 3	Month 6	Year 1	Every 6 mos.
Informed consent	X		X									
Medical Assessment		X	X	X	X		X	X	X	X	X	X
Imaging studies		CT/MRI			CT							
Electrophysiology				X								
Sound Field Thresholds		X					X	X	X	X	X	X
Speech Perception Assessment		X							X	X	X	X
Speech/Language Assessment		X							X	X	X	X
Hospitalized				X	X	X	X					
Adverse Events Reporting				X	X	X	X	X	X	X	X	X

Screening, Informed Consent, and Enrollment

Patients will come from either the UNC Ear and Hearing and pediatric CI practices (>100 new patients/yr.) or from outside the institution. It is anticipated that potential subjects from outside the institution will hear about the study through discussion among colleagues. The records of the UNC children currently in our program and known to have cochlear or cochlear nerve disorders that would make them potential candidates will be reviewed by the principal investigator to identify their potential candidacy. Children with such disorders are currently tracked as a part of the principal investigator's secure patient list in WebCIS (Inner ear malformations list). During a routine patient visit, general interest in the study will be discussed in privacy. Should there be general interest, a detailed (~1 hr.) discussion will be scheduled to go through the entire protocol and consider informed consent. Both subjects that are interested and those uninterested in participation will be tracked and recorded. For those subjects that are not patients of the principal investigator, a knowledgeable individual will provide the subject with information and contact details of the investigator. The prospective subject can then initiate contact, if desired. There are no criteria that limit access among women or minorities. The requirement for participants to be primary English speaking families will limit access among non-English speaking individuals. This is a precondition because the investigators must be able to administer and judge speech and language test results that are English only in nature. This also allows for analysis among similar types of tests materials. Given the small number of participants, this is an unavoidable precondition.

The Principal Investigator will inform the parent or guardian about all aspects of the study for implantation of the Nucleus 24 ABI including: study expectations and requirements, surgical procedure, and the postoperative evaluations and schedule. The risks of surgery and activation will be explained to the parent or guardian as outlined in the Institutional Review Board (IRB)-approved Informed Consent Form. The potential limitations and advantages of implantation with the Nucleus 24 ABI shall also be explained.

The parent or guardian will be given the opportunity to ask questions about the procedures, Informed Consent Forms and the study details prior to signing the Informed Consent Form. The parent or guardian will then be given a copy of the signed Informed Consent Form. For children old enough to participate in the process (7 yrs. and older) of informed consent, they will also be

given an appropriate informed consent form to read and sign as deemed appropriate. Following informed consent, Inclusion/Exclusion criteria will be considered for the prospective subject. If the subject meets criteria, enrollment will be carried out.

Medical History and Physical Examination

This is a standard part of routine medical care. This will include a detailed evaluation as outlined by Buchman et al (49). Additional components unique to this evaluation will include: hearing history, CI history, medical/surgical history, vaccination history, social history, and physical examination. Review of appropriate audiometric and imaging studies will be conducted. The reasons for seeking these pieces of information are detailed below and listed in the Inclusion and Exclusion section above.

Hearing history: Newborn infant hearing screening results, diagnostic auditory brainstem response testing results, as well as etiology, onset, duration, severity, and duration of profound hearing loss will be sought and recorded. The hearing history might identify issues relevant to understanding the etiology of the child's hearing loss. As an example, children with evidence of passing the newborn infant screening and progressive hearing loss might have a degenerative neurological disorder rather than congenital hearing loss. This would be considered a contraindication to implantation (see exclusions). On the other hand, a pass on the newborn infant hearing exam using otoacoustic emissions and present cochlear microphonic on ABR would be consistent with cochlear nerve deficiency. Another important issue might be if a child had normal hearing and development prior to meningitis would be important for understanding the onset and duration of hearing loss.

CI history: Date and hospital of implantation, ear implanted, device type, number of electrodes implanted in the cochlea and activated, duration of use, parental subjective assessment of performance and aversive reactions, date of explantation and reason (if applicable). Understanding these issues are extremely important for better assessing whether the reason for poor performance with a CI is related to the surgical procedure, a potential device abnormality, or the underlying disorder. Potentially, a child with a surgical reason for poor performance might be counseled to consider revision or contralateral CI rather than ABI.

Medical/Surgical history: This will include a comprehensive review of medical conditions (cardiac, pulmonary, renal, neurological, metabolic, etc.) that are known to contraindicate major surgery as well as use of the implant (see Exclusions above). Previous surgical history including anesthetic history, details of CI surgery, and complications will be reviewed. A detailed review of systems will also be carried out and recorded.

Vaccination history: The vaccination history will be carefully reviewed to assure compliance with the recommendations of the Centers for Disease Control (CDC) and the United States Food and Drug Administration (FDA) for individuals with CIs (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5909a2.htm).

Social history: A detailed social history will seek information regarding the parental support, educational and home environment. Specifically, issues related to parental ability to comply with the therapeutic and follow-up expectations of the protocol. This includes the parent's commitment to developing audition skills for their child as a component of their communication strategy.

Physical examination: A thorough physical examination with particular focus on the details of the head and neck, cardiac, pulmonary, and neurological systems will be carried out. CI sites as well as other surgical sites in the head and neck will be assessed. Ongoing otitis media will be identified and treated as needed.

Imaging

The imaging protocols and diagnostic criteria for the various inner ear malformations and CND are in active clinical use in our institution and will be carried out as described previously (27-30, 49). These will include both MRI and CT imaging. For children with a previous CI, the safety and need for MRI will be carefully considered. If previous MRI has been obtained and are of adequate quality, these will be sufficient. If the internal auditory canals (IACs) are very narrow on previous MRI or CT, MRI may also not be needed. If the diagnosis of CND is in question or the brain morphology is has not been adequately assessed, CI magnet removal will be considered prior to scanning. The imaging protocols include:

MR Imaging Protocol. MR imaging is performed with a dedicated pediatric vestibulocochlear nerve (CNVIII) protocol, on either a 1.5T scanner (Sonata, Avanto, Vision, or Symphony; Siemens Medical Solutions, Malvern, Pennsylvania) or a 3T scanner (Magnetom Trio, Siemens Medical Solutions) by using a single- or 12-channel head coil. For young children, this may require general anesthesia. The protocol includes axial and sagittal unenhanced T1-weighted images, axial T2-weighted images, and axial fluid-attenuated inversion recovery images through the entire brain, as well as high-resolution 3D CISS or RESTORE (Siemens Medical Solutions, Malvern, Pennsylvania) images through the temporal bones. Parameters for the CISS sequence varied by scanner (TR/TE/NEX, 5.42–12.25 ms/2.42–5.9 ms/1–2; FA, 50°–80°; FOV, 120–180 mm; matrix size, 256), with resultant near-isotropic voxel sizes ranging from 0.5 to 0.7 mm in length. The RESTORE sequence, which was performed only on the Sonata, was acquired with the following parameters: TR/TE/NEX, 1000 ms/136 ms/1; echo-train length, 21; FA, 180°; FOV, 140 mm; matrix size, 192, resulting in a voxel size of 0.7 mm. In most cases, patients were scanned under conscious sedation or general anesthesia. Total scanning time for each examination was approximately 20 minutes. The temporal bone sequences were reconstructed in the axial plane as well as in an oblique sagittal plane oriented perpendicular to the long axis of each IAC for viewing.

CT imaging protocol. Temporal bone CT scans were performed on either a 16- or 64-slice CT scanner (Sensation 16 or Sensation 64; Siemens Medical Solutions). Contiguous direct sequential axial and coronal images (120 kVp, 200 mAs) are acquired through the temporal bones using a collimation of 0.6 or 0.75 mm.

All MRI and CT images will be reviewed on a clinical picture archiving and communication system (IMPAX 5.0; AGFA, Ridgefield Park, NJ, USA). All quantitative measurements are made using the standard ruler tool included in our picture archiving and communication system software package.

Audiological Assessment

Pre- and Post-operative Behavioral audiometry and speech perception testing. The standard clinical CI speech perception and speech and language test battery will be used. This testing is in common use every day in our clinics. Tests will be presented in a sound-controlled sound booth using monitored live voice (50 dB HL) in the auditory only condition or recorded materials (60 dB SPL). These tests include:

- Detection audiogram, aided and unaided individual ears
- IT-MAIS or MAIS
- LING 6 sound test
- ESP Low Verbal or Standard- MLV @ 50dB HL
- PB-k words and phonemes- MLV @ 50dB HL
- MLNT- recorded @ 60dB SPL If >50% then
- LNT- recorded @ 60dB SPL If >80%, then
- CNC- 50 words @ 60dB SPL
- HINT-C- 2 lists of 10 @ 60dB SPL

Standard audiometric techniques will be performed for measuring sensitivity to sound with the ABI activated. Visual reinforcement audiometry will be performed to measure sound field thresholds up until the child is 30 to 36 months of age. Conditioned play audiometry will be performed when the child is approximately 30 to 36 months of age and older. Stimuli will be delivered via loudspeaker in the auditory only mode consisting of live-voice speech and warbled tones or narrow-band noise for 250, 500, 1000, 2000, 4000, and 6000 Hz. These tests will be used to document profound hearing loss preoperatively as well as the level of sound detection using the device in the post-operative period.

The following speech perception measures are routinely used with CI recipients and represent a hierarchy in both the child's required response and the difficulty of test material. When a child is not able to participate in structured testing for any reason including age, attention, or level of auditory development, then a parental questionnaire is used (IT-MAIS or MAIS). The earliest developmental response format is detection and imitation (LING 6-sound test), followed by a small (4 items) closed-set format (ESP-low-verbal) and then a larger (12 items) closed-set format (ESP standard). Open set speech recognition follows (PB-k, MLNT, LNT). Each child will be assessed starting with the lowest level of the battery at each assessment interval until a 100% score is achieved at 2 consecutive test intervals. Criteria for moving on to the next test are based on the child's developmental (behavioral and auditory) skills, not chronological or hearing age.

Meaningful Auditory Integration of Sound (MAIS) and Infant-Toddler Meaningful Auditory Integration of Sound (IT-MAIS) (51, 52). The MAIS is a 10-item parent-report scale designed to evaluate developing auditory behavior in children ages 4 years and older. Parents rate how often their child engages in specific behaviors with regard to their child's bonding with the sensory device, auditory awareness, and the ability to derive meaning from sound. The IT-MAIS was developed for children younger than 4 years. While it shares the majority of questions with the MAIS, the IT-MAIS additionally explores vocal behavior of infants with their sensory device. The MAIS probes ten questions in a structured parent interview,

assessing the child's bonding with the sensory device, auditory awareness, and ability to derive meaning from sound in everyday situations.

Ling Six Sound Test (Ling, 2002/2003). The Ling Six Sound Test samples the child's ability to detect and identify speech sounds representative of the speech frequency spectrum (ah, oo, ee, sh, s, m). The test is administered live-voice.

Early Speech Perception (ESP) Test (53). The ESP is designed to assess pattern perception (differentiation of syllable number and stress pattern), spondaic word identification (two syllable word with equal stress on each syllable), and monosyllabic word identification in a closed-set. Attainment of a criterion level is required to pass each sub-test. This test is generally introduced when the child is 2 years of age or when he or she is able to choose between two alternatives. There is a standard version and a low-verbal version. Stimuli for both versions are typically presented live voice.

Multisyllabic/Lexical Neighborhood Test (MLNT/LNT) (54). The MLNT and LNT are open-set tests that explore the lexical properties of spoken word recognition. The words are divided into easy and hard lexical categories based on word frequency and phonetic similarity. The stimuli consist of multisyllabic words in the MLNT and monosyllabic words in the LNT.

Phonetically Balanced Kindergarten Word Test (PB-k) (55). The PB-k is an open-set test of 50 words that are meant to represent the distribution of phonemes in English using kindergarten level vocabulary. The child repeats the word and his responses are scored for the correct word and number of phonemes repeated. This will be presented in a monitored live voice mode.

Consonant- Nucleus-Consonant Word Test (CNC) (56). The CNC is an open-set test which includes 10 lists of 50 words recorded by a male speaker. This test was developed to provide lists of monosyllabic words with equal phonemic distribution across lists with each list exhibiting approximately the same phonemic distribution as the English language.

Children's Hearing in Noise Test (HINT). The HINT test is made up of 12 lists of 10 sentences; each sentence is 5 to 7 words in length. The child repeats as much of the sentence as possible and points are given for key words repeated. Noise may be added to this test to increase its difficulty.

Speech and Language Assessment

Communication mode and educational setting are identified and recorded by the managing audiologist and/or speech pathologist at our institution. The following tests will be administered in their standardized forms. The raw scores will be used to compare children to their chronologically aged peers with typical hearing to determine standard scores by following testing protocols. Results will be discussed using comparative measures to the subject's hearing age with the ABI as well. Our protocol for speech-language evaluations are well established for our population with CIs despite very little time with usable hearing. This same protocol will be used to effectively assess children's spoken language development with an ABI. There are at least 2

dedicated speech pathologists on the pediatric CI team with extensive experience using these measures in children within the proposed age range. The standard clinical test battery includes:

MacArthur-Bates Communicative Development Inventories (CDIs) (57). CDIs are parent-report instruments designed to evaluate early receptive and expressive language skills in children. The CDI/Words and Gestures assess vocabulary comprehension, production and the use of gestures typically used by children in the 8-to-18 month age range. The CDI/Words and Sentences extend the list of vocabulary words and probe a number of aspects of grammatical development typically acquired by 30 months of age.

Pre-School Language Scale, Fourth Edition (PLS-5) (Zimmerman, Steiner, & Pond, 2010). The PLS-5 is a standardized language test designed for infants and young children. The Auditory Comprehension subscale targets skills known to precede language development, including: attention to speakers, appropriate object play, basic vocabulary, concepts, grammatical markers, and complex sentences. The Expressive Communication subscale assesses vocal development, social communication, naming of common objects, phonological awareness, sequencing skills, as well as use of concepts, prepositions, grammatical markers, and varying sentence structures.

The Oral and Written Language Scales (OWLS) (Elizabeth Carrow-Woolfolk) The OWLS assesses the comprehension and expression of language of children 3 to 21 years of age. This test examines an individual's ability to understand and produce connected language looking specifically at vocabulary, grammar, pragmatic function and higher order structures of language.

Goldman-Fristoe Test of Articulation. (Goldman-Fristoe, 1986).This test assesses a child's articulation ability by sampling both spontaneous and imitative speech production. Pictures and verbal cues are used to elicit single word answers that demonstrate common speech sounds. The Goldman-Fristoe measures the articulation of speech sounds and identifies and describes the types of articulation errors produced by the child.

Surgery

Nucleus Multichannel ABI will be placed using the retrosigmoid craniotomy on the side opposite the child's previous CI (when present) and assuming there are no obvious contraindications. This approach provides direct access to the lateral recess of the 4th ventricle and region of the cochlear nucleus. This approach has previously been documented to be safe in the literature for this use (48) and has been used extensively in adults and children at our institution for other causes. Our team has extensive experience with cerebellopontine angle surgery (i.e. the region of interest). In 2009-2011, we carried out 71 cerebellopontine angle craniotomies for acoustic neuromas (16 retrosigmoid). In that time period, there were a total of 120 retrosigmoid craniotomies in adults and 42 in children. We have also carried out the only retrosigmoid approach for ABI placement in an adult patient without NFII in the United States to date (see images and description below).

Surgery is carried out under general endotracheal anesthesia, without paralytic agents, and is administered by a pediatric anesthesiologist in a children's hospital operating room. The child

will have 2 large bore intravenous catheters placed. Following induction, the child will be maintained under normotensive anesthesia using a combination of inhalational and intravenous agents. The auditory monitoring montage will be placed as described below. Cranial nerve electromyography monitoring will consist of bipolar, needle electrodes placed in the ipsilateral facial muscles (orbicularis oris and oculi-CN VII), soft palate (CN IX-X), and trapezius (CN XI). Appropriate monopolar needle electrodes will serve as ground and stimulating electrodes and will be placed in the pre-sternal subcutaneous skin. The NIM-Response® 3.0 (Medtronic, Minneapolis, MN) nerve integrity monitor will be used to continuously monitor EMG activity under both spontaneous conditions as well as under evoked testing.

The patient will be positioned in an age appropriate head holder in a modified lateral position to expose the suboccipital cranial region. An appropriate location for the receiver stimulator will be identified based on the device templates and marked with injection of methylene blue on to the skull in a routine fashion. A post-auricular incision will be marked and infiltrated with 1 lidcaine and 1:100,000 epinephrine solution. Monopolar cautery will be avoided to protect the child's previous CI. Following skin flap creation, the region of the retrosigmoid craniotomy will be exposed based on standard surgical landmarks (asterion, inion). A standard, retrosigmoid craniotomy (~2.5 x 2.5 cm) will be created, exposed mastoid air cells occluded with bone wax and the suboccipital dura exposed.

Dural incisions will open the posterior cranial fossa and using the operating microscope, CSF is drained from cisterna magna and the lateral cerebellopontine angle cistern with gentle retraction. The posterior-ventral and dorsal cochlear nucleus is the most accessible portion of the nucleus complex for electrical stimulation. These structures are located on the anterior surface of the lateral recess of the 4th ventricle and can be visualized. After cerebellar relaxation, the lower cranial nerves are identified and the IX cranial nerve and choroid plexus emanating from the Foramen of Luschka will be viewed with gentle retraction of the cerebellar flocculus. The facial nerve, ventral to the lateral recess and cochleovestibular nerve and/or its remnant as well as the lower cranial nerves exiting inferiorly are identified and confirmed with stimulation. Opening the recess arachnoid may reveal the choroid plexus and can release CSF to aid in identification. Upon opening the recess, the cochlear nucleus prominence is evident on anterior wall.

The receiver-stimulator of the Nucleus 24 Multichannel ABI will be seated in a depression on an appropriate site on the skull, based on methylene blue markings placed prior to incision. The receiver-stimulator will be immobilized with periosteal sutures and a trough for electrode immobilization created if skull thickness permits. The array will be advanced in to the recess with the array facing the nuclear prominence as shown in Figure 1 below and Teflon® felt used to secure the array. The separate ground, ball electrode will be advanced under the temporalis muscle periosteum in a standard fashion. Electrophysiologic testing will then commence as described below. If testing confirms responses on a number of electrodes, closure will commence. If testing does not reveal responses, exploration will be undertaken to again confirm location.

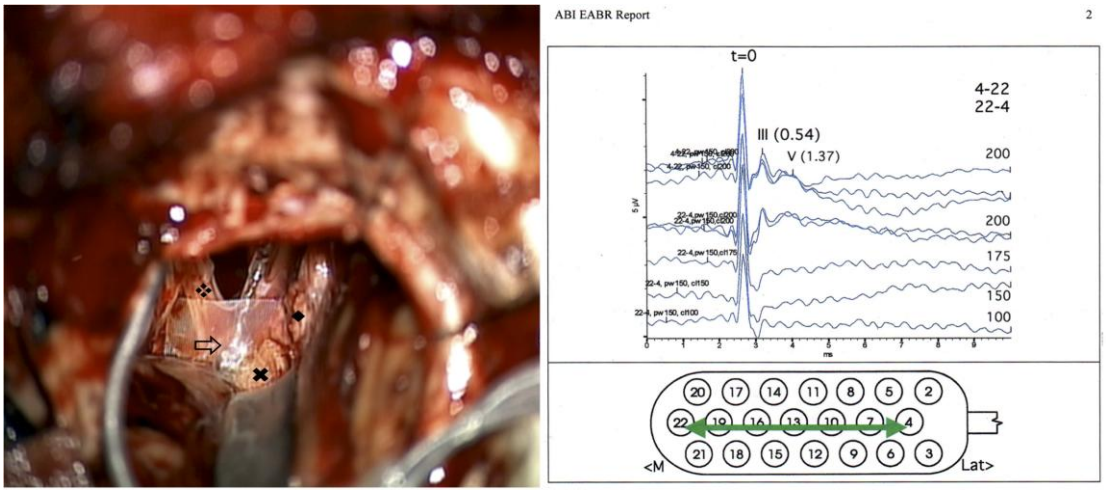

Figure 1. Intraoperative image (left) from an adult patient with a history of post-meningitis hearing loss and severe cochlear ossification that failed CI and underwent left retrosigmoid craniotomy with insertion of a Nucleus 24 Multichannel ABI at UNC-Chapel Hill in 7/2007. Responses recorded from implant stimulation are shown on the right. The left image shows the ABI array in place (⇧), normal choroid plexus (◆), 8th cranial nerves behind the electrode wire, and 9th nerve (❖) entering the lateral recess of the 4th ventricle. The implant array is seen exiting the recess and Teflon® felt (✖) is seen securing the position of the electrode array.

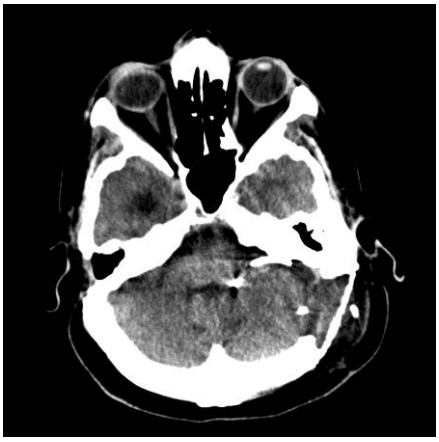

Figure 2. Postoperative CT image of the patient above showing Nucleus 24 Multichannel ABI well positioned in the lateral recess of the 4th ventricle.

Intraoperative Electrophysiology Testing

Intraoperative electrically-evoked auditory brainstem response (EABR) testing is undertaken to provide electrophysiological information concerning device placement and functionality. The primary electrode montage for EABR testing is midline, with the non-inverting electrode at Cz (vertex), the inverting electrode at C7 (cervical vertebra 7), and the ground electrode at the nape-of-neck (hairline). A discretionary duplicate set of electrodes can also be placed with the non-inverting electrode at Fz (high forehead), the inverting electrode anterior to the tragus on the ear contralateral to the surgical side, and the ground electrode at Fpz (mid-eyebrows). In all cases, electrodes are 15-20 mm subdermal needle electrodes sutured in place or

otherwise fixed with tape. All electrode leads are labeled, braided together, and positioned away from the surgical field with their terminals accessible. Electrode placement necessarily occurs during the preparation of the patient for surgery, and it is recommended that the impedances of the electrodes be measured at the time of placement to ensure optimum connectivity.

Following device placement, a series of bipolar stimulations are undertaken in an effort to elicit auditory-evoked responses. In general, initial electrode pairings for bipolar stimulation are transverse across the length of the device (see schematic of electrode pad in Figure 1b), with subsequent pairings honing in on more spatially localized stimulation, as dictated by the pattern of results and available testing time. The objective is to grossly map out the regions of the electrode pad that are conducive to auditory stimulation. This mapping allows interpretation in terms of placement/orientation of the electrode pad relative to the surface of the cochlear nucleus, and may guide device re-positioning decisions.

Stimulation parameters for this mapping process are optimized for auditory-evoked responses. Typical parameters include biphasic pulses (150 μSec/phase) presented at a rate of 35 Hz at a level of at least 150 CUs. When responses are observed, pulse polarity should be reversed to confirm the neural basis (see sample traces in Figure 1b). Stimulation is provided through the NRT Nuclear Response Telemetry system from Cochlear Ltd. using the Portable Programming System (PPS). For this testing, the head coil is placed within a sterile sheath and positioned over the receiving antenna of the implant. The PPS is connected to a Sprint speech processor that is stimulated by the Nucleus programming software NRT 3.1. The PPS also provides a TTL trigger to synchronize the EABR recording system. These systems are approved for use as a part of the Nucleus 24 ABI System.

The recording parameters are optimized for EABR recording. Typical parameters include wideband recording filters (e.g., 100 – 5000 Hz), 10-mSec recording window, amplifier gain of X100,000 with artifact rejection turned off. Number of averages is dictated by the quality of the response and is typically set to 500-1000.

Surgical Closure

Once the array is optimally placed, the dura will be closed with interrupted sutures. As the closure cannot be completely watertight owing to the cable from the array, abdominal fat may be harvested and used to create a watertight closure. The bone flap if present can be replaced with titanium mesh and screws or a complete mesh cranioplasty may be placed.

Postoperative Care

Following surgery, the child will be admitted to a specialized pediatric intensive care unit (PICU) in the North Carolina Children's Hospital. The unit is staffed full time by pediatric intensive care specialists with expertise and experience in pediatric neuro-intensive care. The child is monitored continuously using both invasive and non-invasive methods as needed. These may include an arterial line, central venous pressure (CVP) line, urinary catheter, blood pressure, pulse oximetry, EKG, and continuous nursing observation. It is anticipated that the child's endotracheal tube will be removed early in the postoperative period, either in the operating room or while in the PICU. Ventilator support as well as pain control and adequacy of sedation will be

closely monitored while an endotracheal tube is indwelling. Intravenous antibiotics will be administered for a no more than 24 hours following surgery in accordance with current recommendations from the American Association of Neurological Surgeons (AANS) and the American College of Surgeons (ACS). If the patient is allergic to penicillin or the cephalosporins, vancomycin will be administered intravenously for 24 hours. The pharmacy will be consulted for specific dosing based on the patient's weight. Corticosteroids will be administered for approximately 2 weeks or less following the surgery to minimize any brains swelling. Pain medication will be given prophylactically early on and as needed in the post-operative period. A CT scan will be obtained on the first postoperative night to evaluate for brain swelling and electrode array location (Figure 2 example). The patient in mobilized, and diet is advanced on the first postoperative day as tolerated. Intravenous fluids are weaned as oral intake increases.

The child is discharged from the PICU to a standard pediatric surgical floor no sooner than postoperative day 1 (day after surgery) or later as medically indicated. De-intensification includes removal of the urinary catheter, and discontinuation of continuous EKG and oximetry monitoring. On day 3 following surgery, the incision will be examined for CSF leakage. In the absence of a leak, the child will be discharged home with instructions for the parents to follow-up in one week as an outpatient. Appropriate phone numbers are provided for the clinics, hospital, and emergency department as well as details that should prompt the family to return to the hospital. These would include: increasing pain, swelling, nausea, vomiting, fever, shortness of breath, rapid breathing, changes in mental status, or anything that concerns the parents.

Should the child develop CSF leakage from the wound, over-sewing will be carried out as a sterile procedure. Should the child develop rhinorrhea, surgical re-exploration of the wound or lumbar subarachnoid drainage will be undertaken depending on the age and cooperativeness of the child and the presence and violation of the mastoid air cells that were observed at the time of surgery.

Initial Activation and Follow Up Testing

At the initial stimulation and at subsequent device programming sessions, a combination of objective data and behavioral methods will be used to program the speech processors. Data gathered from intra-operative electrophysiological testing that identified electrodes with optimal responses to stimulation would be selected for inclusion in the speech processor program. As with the initial stimulation of CIs in young children, behavioral observation and conditioned behavioral audiometry techniques will be used to determine electrical thresholds and comfortable listening levels. The initial stimulation will take place in the ENT clinic with pediatric anesthesia support. Starting with electrode pairs that elicited the best, evoked responses in the OR, stimulation will commence in a conservative fashion, using an ascending approach, until a behavioral response is observed. It will be documented when stimulation awareness is observed. Depending on the child's level of cooperation, conditioning of that response will ensue. During the initial stimulation and subsequent programming sessions, the child will be trained to participate in device setting. If stimulation levels result in visible or aversive responses (facial contraction, throat tickle, cough, shoulder activation, extremity sensations) higher stimulation levels will not be attempted. Although young children who have no auditory experience are limited in their ability to provide feedback about stimulation, our team of pediatric CI

audiologists has extensive experience in monitoring behaviors and interpreting responses to auditory electrical stimulation from children as young as 9 months of age on a routine basis. It is anticipated that the programming of the speech processor for the ABI will be similar in practice to programming CIs using a progressive mapping approach which includes making incremental changes to current levels over time, allowing for comfortable adaptation to sound. Only programs that have been stimulated in the clinic will be programmed to the user speech processor. The children will be seen at the designated follow up appointments for device programming at 4 weeks post initial stimulation and at 3, 6, 12, 18, 24, 30, 36 months for mapping and assessment including behavioral audiometry and speech perception testing. A language assessment will be repeated at 6-month intervals.

Data and Analysis

A single-subject research design was chosen (in which each subject serves as their own control) in order to accommodate for the heterogeneity that is well known to characterize auditory prosthesis research. Post-operative evaluations will be conducted at the initial activation and at 1, 3, 6, 12, 18, 24, 30, and 36-month intervals post-activation. Blinding or masking procedures are not included in the design, as the presence/absence of a brainstem implant cannot be easily concealed from the device recipients and/or clinical investigators.

Data will include demographics, frequency of both major and minor complications as well as audiometric and speech and language data. The summary statistics will be reported on the various categorical (gender and complications) and continuous (age, audiological and speech perception, production and language scores) variables.

Baseline audiological and speech perception, production and language measures taken prior to ABI surgery will be compared to scores at each follow up interval within each subject. For subjects with no response on behavioral testing, a maximum score of 120 dB HL will be assigned at the test frequency as this represents maximum stimulus levels of the equipment. Pure tone average (PTA) is calculated using the thresholds from 500, 1,000, and 2,000 Hz. When speech perception testing is limited by short duration experience or young age, inattention, or the presence of significant comorbidities, these reasons will be recorded. When inability to complete the test is evident despite significant implant experience, the patient is assigned the value for chance correct responses for the appropriate test (i.e., 0% for open-set tests or 33% for ESP pattern-[P] perception tests). When a child advances out of a particular measure because of ceiling effects, then the next measure will be undertaken. For children able to perform a given speech perception measure(s) prior to ABI surgery, that measure(s) will be repeated at the initial post-operative visits to insure the same test comparisons exist. It will be assumed that children that are unable to perform closed set testing will not be able to perform open set testing at a given visit. Thus, scores on these tests will be assigned the value of “unable to test”.

Change values for each of the variables will be calculated by subtracting off baseline values when available. The mean percent change at the various intervals for each variable can be averaged (+/- SD) across the subjects. Comparison to baseline measures for significance testing will be made with 95% confidence intervals when possible. The chance that this is not possible exists because of the broad variation in ages and possible achievements with the device.

For speech perception, there is a developmental hierarchy that is required to evaluate the emergence of this skill over time. This will be tracked and plotted on a graph against similar children with normal hearing as well as those fitted with CIs with and without malformations for comparison (30, 50). This modified cumulative speech perception index in quiet (SRI-Q) will be created after Wang et al. (50) and Buchman et al (30) in an effort to simultaneously display the data from all tests in the speech recognition hierarchy as a function of time. ESP-P is considered easier than ESP-monosyllabic (M) words. CNC word scores then follow PB-k word scores. The measured percentage score for each test (0%–100% correct) is then hierarchically ranked and stacked in 100-point increments. These results are controlled for duration of device usage and age at implantation. Speech production and language data are reported as age-normed values and will be compared to children of a similar age with normal hearing as well as those using CIs.

It is anticipated that this pilot study will be used to demonstrate safety and give some idea regarding efficacy. However, a larger scale clinical trial will be needed beyond the pilot study to demonstrate surgical safety on a broader scale (across surgeons and institutions) and the utility of the device for the intended auditory benefits. Ten subjects should be a sufficient sample size to demonstrate safety. If the European data is correct regarding complication rates in children, a single CSF leak might occur in one subject and non-auditory side effects can be expected to occur in roughly 20% of children or 2 subjects in this study. This number seems to be a conservative and reasonably small number to demonstrate these effects. Non-auditory stimulation is not serious and can be programmed around with simple changes in device programming during activation. For speech perception and production, the within subject design should allow us to see some benefit from the device if effective. Since the children are deaf, any development of significant open or closed set perception (beyond patter perception) would be attributable to the device. Similarly for language outcomes although these will take longer time to develop. Thus, the safety numbers are the drivers in powering this study.

The data will be recorded in patient-specific binders on a case-by-case basis after each subject encounter. All data will be entered in to the secure, File Maker Pro, customized database for CI research housed in the Department of Otolaryngology-Head and Neck Surgery that is currently in use. The lead investigator will cross check the data prior to approval for review. The data will be exported by desired fields to an Excel spreadsheet (Microsoft) for further analysis. Statistics will be carried out using SPSS software. If needed, statistical consultation will be sought at the University TRACS or Odum Institute.

Study Endpoints

Study endpoints are based on the 3 specific aims. For safety, this will be determined on a case-by-case basis and any adverse events will be reviewed with the IRB and the data monitoring board (2 individuals appointed). Should the adverse events be deemed unacceptable to the investigators, the IRB, or the monitoring board, this would be sufficient terms for study discontinuation. Three years of follow up was chosen to provide adequate time for the emergence of open-set speech perception abilities in the pre-lingual cohort of children. In studies of prelinguistic children undergoing CI, at least 2 years of follow-up is needed to demonstrate emergence of these skills (23). If no open set perception is demonstrated at 3 years, this seems to be good evidence for a lack of benefit on this measure. In general, speech and language measures should track speech perception abilities. While the full emergence of these skills can take

somewhat longer to develop, it is anticipated that early emergence will be evident if speech perception is developing. While not anticipated, a clear lack of benefit from the device (such as no sound awareness) among multiple subjects would also be consideration for stopping the study. Study recruitment is expected to be slow at 1-3/year. This will not stop the study.

Human subject protection measures

Risks and measures to minimize risk. There is limited psychological, social, legal and economical risk to patients for participating in this study. The potential for a confidentiality breach is rare. All children and their parents will be treated confidentially according to HIPAA and its requirements. All discussion of the results of the intervention for the purposes of results reporting will be made anonymously.

The physical risks include medication side effects, pain, discomfort, or injury from participation. The potential risks from participation are likely (10-25%) and dependent on the consequences in question. The potential complications have been detailed above.

Complications related directly to the ABI have been unusual. Toh and Luxford indicated the most common complications in ABI surgery appear to be cerebrospinal fluid (CSF) leak, electrode migration, and non-auditory side effects during stimulation. There have been no fatalities related directly to the placement of the ABI. Rather, mortality has occurred in patients treated for brain tumors from NFII in the same location where surgery was prolonged and the patients developed pulmonary embolism post-operatively. Electrode migration appears to be a complication that occurs in patients undergoing ABI in the setting of tumor removal where distorted brainstem anatomy results in a shallow or deformed lateral recess. Following surgery, brain re-expansion might displace the electrode.

CSF leaks are an expected risk from any surgery where CSF cisterns are entered. Otto et al reported 2 CSF leaks among 61 patients following translabyrinthine tumor removal and ABI placement that resolved with either a pressure dressing or a temporary lumbar subarachnoid drain (47). Grayelli et al. also reported 2 cases of CSF leaks after 31 ABI surgeries and Sennaroglu et al. reported one case of a CSF leak in a child who underwent retrosigmoid ABI placement that resolved with would exploration and repair of the air cell opening (42, 43).

Colletti et al reported on 114 ABI operations performed through the retrosigmoid approach in Verona from 1997 to 2008 in 83 adults and 31 children (48). Thirty-six had NFII (34 adults and 2 children), and 78 (49 adults and 29 children) had cochlear or cochlear nerve disorders unrelated to NFII. The table on page 7 details the complications from this study. There was a statistically lower risk for complications among the patients without NFII, presumably because there was no need for tumor removal prior to device placement. Importantly, there was 1 major complication in a child implanted in Manchester, England. That child developed a cerebellar contusion and swelling requiring a return to the operating room for evacuation. This child recovered without neurological sequelae.

Other complications in children included wound seroma (n=4) that were managed with aspiration and bandage, minor wound erythema treated with antibiotics alone, and transient balance problems that resolved without treatment.

Non-auditory side effects are a relatively common occurrence from ABI stimulation and are usually related to activation of the neural tissue in the region of the implant. Toh and Luxford reported non-auditory side effects in 42% of multichannel ABI users following tumor removal in NFII patients (44). Colletti et al (48) reported ipsilateral body tingle was observed in 2 children (6.9%), facial nerve stimulation in 2 (6.9 %), dizziness in 1 (3.4%), headache in 1 (3.4%), and throat tingle/tickle in 1 (3.4%) child. In adults, ipsilateral body tingle was observed in 10 subjects (8.7%: 7 NFII and 3 non-tumor), facial nerve stimulation in 6 (5.2%: 4 NFII and 2 non-tumor), dizziness in 15 (19%: 9 NFII and 6 non-tumor), headache in 5 (6 %: 3 NFII and 2 non-tumor), and throat tingle/tickle in 8 (9.6%: 5 NFII and 3 non-tumor). These side effects are all alleviated with selective electrode deactivation. Re-activation of the offending electrode over time usually resolved the issue.

In summary, discomfort from non-auditory stimulation seems likely although in children the risk appears to be less than 20%. The other complications are very unlikely or infrequent. Pain following surgery is probably an expected occurrence that will be managed with pain medication. The risk of long-term headache seems rare.

Data and safety monitoring. Subjects will be monitored on a case-by-case basis for ongoing or unanticipated medical complications. Adverse events will be tracked on a case-by-case basis and recorded in study binders at the time of occurrence and followed up at resolution. Any adverse events will be reported to the IRB. Should there be concern for the safety of the subjects because of their participation in the study by the investigators or the IRB, the study would be halted at least temporarily and a detailed discussion with the investigators and the IRB would be undertaken to evaluate the viability of the study. Two chosen experts in the field will also review serious adverse events as external reviewers.

- Thomas J. Balkany, MD Professor and Chairman Emeritus, Department of Otolaryngology-Head & Neck Surgery, University of Miami, Miami, FL. Email: tbalkany@med.miami.edu
- J. Thomas Roland, MD Professor and Chairman, Department of Otolaryngology-Head & Neck Surgery, New York University, New York, NY. Email: John.Roland@nyumc.org

Unanticipated adverse device effect (UADE) is defined as 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 that was not previously identified in nature, severity, or degree of incidence in the literature or investigational plan. It can also include any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

As required by 21CFR 812.150, the sponsor will report any UADE to the FDA within 10 days of learning of the event, and to the local IRB per institutional guidelines.

Participants or their families can withdraw from the study at any time by notifying the primary investigator. If the investigator identifies the need to withdraw a participant from the study for any reason, this will be discussed in person during a scheduled evaluation. The subject will still receive ongoing care irrespective of their participation in the study. Should the subject not be able to use their device, or develops complications related to participation in the study,

their participation in the study will end when their study related morbidity has resolved or is no longer active. Again, this will not affect the ongoing medical care for the subject.

Ongoing morbidity and adverse events deemed unacceptable to the investigators, the IRB, or the external reviewers would be sufficient terms for study discontinuation. Moreover, a lack of benefit from the device among multiple subjects would also be consideration for stopping the study. Study recruitment is expected to be slow at 1-3/year. This will not stop the study.

Confidentiality of the data. Subjects will be assigned a specific, anonymous participation code that will be associated with their particular data file. Database entry will be by participation code only. All personal identifiers will be kept in a separate, secure data file that will be password protected and not associated with the primary data. Only the principal investigator will have access to these codes.

Patient specific binders will be kept in a single location in a locked cabinet. Individual data collection sheets will be coded and placed in the patient-specific binders immediately after coding. For analysis, the data will not include specific personally identifiable names, dates of birth, medical record numbers, etc. (PHI).

Given the pilot nature of the project and the relatively small number of subjects and anticipated occurrences, deductive disclosure is possible if a subject experiences a unique adverse event that other investigators are aware of. There will be limited to no potential for those outside the study to deduce the identity of the subject unless they were somehow associated with them personally. Data will not be shared outside the primary investigative team except during reporting of results anonymously.

Data will be stored in a locked file cabinet until the time the study is closed and then it will be shredded and destroyed in a HIPAA compliant manner. There are no human or biological specimens.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify research subjects.

Institutional Review Board

University of North Carolina Biomedical Institutional Review Board (IRB)
Co-Chairs: Ina Friedman, J. Herbert Patterson, David Weber, J. Douglas Mann,
Address: Medical School Building 52, University of North Carolina - Chapel Hill
Mason Farm Road, CB #7097
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Attached

- Informed Consent and Assents
- HIPAA Authorizations
- PMA Letter
- Device Description

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