Published in final edited form as:

Ther Innov Regul Sci. 2015 September ; 49(5): 659–665. doi:10.1177/2168479015599559.

Regulatory and funding strategies to develop a safety study of an auditory brainstem implant in young children who are deaf

Laurel M. Fisher, PhD¹, Laurie S. Eisenberg, PhD¹, Mark Krieger, MD², Eric P. Wilkinson, MD^{3,4}, Robert V. Shannon, PhD¹, and the Los Angeles Pediatric ABI Team

¹Keck School of Medicine of University of Southern California, Department of Otolaryngology – Head and Neck Surgery, 806 W. Adams Blvd., Los Angeles, CA 90007

²Chief, Medical Staff, Division Chief, Pediatric Neurosurgery, Billy and Audrey Wilder Endowed Chair, Children's Hospital Los Angeles, 4650 Sunset Blvd., Los Angeles, CA 90027

³Huntington Medical Research Institutes, 734 Fairmount Ave., Pasadena, CA 91105

⁴House Clinic, 2100 W. Third St. #111, Los Angeles, CA 90057

Background

Bilateral profound hearing loss identified in infants is a potentially treatable condition with cochlear implantation, if normal inner ear anatomy can be visualized on CT and/or MRI. However, if imaging reveals a lack of a cochlea or cochlear nerve, a cochlear implant is usually contraindicated [1, 2]. Currently, no other surgical treatment options are available in the United States (US) if a cochlear implant fails to provide benefit. Congenital deafness is relatively rare, affecting from 1 to 6 of 1,000 newborn infants [3]. Deafness secondary to abnormal inner ear anatomy is less common, estimated at 20–30% of deaf infants [4].

Anatomically, sound information is relayed from the inner ear (cochlea) via the cochlear nerve to the cochlear nucleus in the brainstem. If the nerve is missing, an auditory brainstem implant (ABI) allows for electrical stimulation of the cochlear nucleus. In 2000, the ABI was approved for profound deafness secondary to Neurofibromatosis 2 (NF2) [Cochlear Corporation, Nucleus 24, PMA P000015]. The ABI consists of both internal and external components (Figure 1). The internal ABI electrode array, with 21 separate electrode contacts, is placed directly over the cochlear nucleus on the brainstem. Sounds are transduced to electrical signals and digitally processed by an external speech processor. The digitized signal is transmitted to an internal receiver/stimulator and routed to the electrode array on the cochlear nucleus. After a healing period, the ABI processor is programmed by an audiologist. FDA labeling indicates that adults and children aged 12 years old and older could be implanted during surgery to remove a NF2-related tumor compressing the auditory nerve. The audiological outcomes in NF2 patients are not as impressive as the outcomes for deaf individuals with cochlear implants. ABI patients with NF2 show some benefit, such as

Corresponding author: Laurel M. Fisher, PhD., Keck School of Medicine, 806 W. Adams, Los Angeles, CA 90007, laurel.fisher@med.usc.edu.

The authors report no conflicts of interest with respect to the research reported herein.

sound detection, but a limited number are able to recognize speech sounds without visual cues [5, 6].

Starting in 2000, surgeons in Europe, and then Turkey, performed ABI surgeries in young children (e.g., age 3) who did not have inner ear anatomy to support the use of a cochlear implant. The treatment goal was to provide access to sound during the critical auditory development [7, 8]. With the ABI, these children experienced environmental sound awareness and some achieved moderate levels of auditory-only word recognition (from a small set of words or “closed-set”) [9, 10].

In patients with NF2, the ABI is placed during a medically necessary craniotomy, thus, the patients experienced little, if any, increase in surgical risks. ABI use in otherwise healthy young, albeit deaf, children involves elective neurosurgery, with consequent increases in risk. Device implantation is not the only safety concern. Electrical stimulation of the device may activate surrounding structures in the brainstem, causing non-auditory side effects (NASEs). In NF2, NASEs include tingling/tickling along the implant side of the body, a feeling of eye twitching, dizziness, facial stimulation, and throat tightness [11]. These NASEs are experienced during electrode stimulation and do not continue without stimulation [5, 12, 13]. Some NASEs are likely due to the brainstem deformation from NF2-tumors. It is not clear what types of NASE young children, who do not have intracranial tumors, would experience.

Worldwide, with nearly 15 years of experience with the ABI in pediatric patients, the ABI is an accepted treatment option [8, 14–17]. A path forward for US FDA approval is less clear. In addition to our center, three US centers expressed interest in submitting an investigational device exemption (IDE) application to the FDA. The Los Angeles team consists of a scientist who led the NF2 ABI clinical trial (RVS), which resulted in FDA approval and an investigator on the original cochlear implant study leading to FDA approval (LSE). The team includes a neurosurgeon who has implanted the ABI in over 50 NF2 patients, an experienced pediatric neurosurgeon, and a neurotologist. The only audiologists with experience programming the speech processor from both manufacturers of the ABI (Cochlear Corporation and MED EL) in both NF2 and non-NF2 settings complete the team. The present article describes the challenges this highly experienced clinical team has faced, negotiating the regulatory, scientific, clinical, and federal funding arenas, when developing a cutting-edge translational clinical trial.

Pathway for study protocol approval and funding

We elected to approach the FDA with a pre-IDE (FDA Guidance on IDE Policies and Procedures, January 20, 1998) and, if indications were positive, to seek federal funding of the clinical trial in parallel with the full sponsor-investigator IDE submission. The pre-IDE mechanism was developed in response to the FDA Modernization Act of 1997 to move clinical trials more quickly through the FDA review process. The process encouraged sponsors and sponsor-investigators to communicate early and often with the FDA reviewing division during protocol development. The conversation between sponsor and FDA focused on problematic areas for resolution without prejudice. The pre-IDE was logged in the FDA

document tracking system and has a 60-day response period, after which protocol modifications may be made.

The pre-IDE review process raised the possibility of approaching the IDE as an early “feasibility study” (FDA Guidance, October 1, 2013). According to the Guidance Document, feasibility studies of significant risk devices were to “obtain *initial* insights” (emphasis in original) into various safety and practical issues related to device use. The research goals were necessarily more limited than a pivotal clinical trial (e.g., cannot rigorously determine statistically significant efficacy), but the results of which could drive the research forward [18]. Feasibility study results will inform the next stage of research and refine clinical trial procedures, indicating which safety-related procedure could be modified, left out altogether, or was essential.

Initial, informal conversations with the FDA revolved around surgical safety issues of a retrogmoid craniotomy in a child as young as 2 years. ABI device-related issues, about which little was known, included: clinician use of the device (programming the electrical stimulation of the electrode), obtaining information about anatomical limitations of device placement in the brainstem of young children, and patients’ everyday use of the device. An early feasibility study generally enrolled 10 or fewer subjects, a reasonable enrollment goal for our sponsor-investigator team. Our study nicely fit the FDA’s criteria, as little was known about implantation of the device in young non-NF2 children.

In response to the FDA’s concerns, the team proposed, and the FDA accepted, a cautious approach to total enrollment and the pace of enrollment. Only 10 subjects were proposed, with a thorough review of all data to occur after the 5th implanted subject finished the 12-month post-surgical period. At that time, all data would be sent for review by the FDA (and the local Institutional Review Board), to ensure that no safety issues would go unnoticed. If the safety data were promising, the study could proceed. The study was designed in the interests of transparency and to slow the tempo of study enrollment to a pace that allowed for a deliberative approach to data collection and interpretation.

One example of a risk mitigation procedure developed through the pre-IDE process concerned the issues surrounding electrically stimulating the brainstem of a patient who had minimal language skills. The interaction between the audiologist and patient during electrical stimulation was critical for avoiding electrodes with NASE. The team proposed that the first ABI activation visit, with an awake and mobile child, would occur in a setting with pediatric advanced life-support (PALS). The presence of PALS-trained personnel and equipment addressed the risk of stimulating brainstem structures responsible for breathing or heart rate regulation. The protocol was further altered, in response to the device programming clinical challenges, to include a 1-month post-implantation activation under sedation. With the close observation of the child by the electrophysiologist/audiologist, anesthesiologist, and neurosurgical team, the child could be monitored for NASE and electrodes with a high likelihood of associations with stimulating the auditory pathway.

Risk mitigation was not sufficient for a successful IDE; some indication of device benefit was critical. Demonstration of potential benefits started with a review of the current

knowledge about pediatric patients' cochlear implants benefit. The cochlear implant was FDA-approved, in 2000, for children as young as 12 months old. Efficacy studies indicated that radiological evidence of inner ear abnormality (bilateral absence of a cochlea, cochlear nerve aplasia/hypoplasia) was associated with the potential for reduced audiological benefit from a cochlear implant [19, 20]. If the child had an additional disability, such as autism or CHARGE, audiological benefit was further reduced [21].

The team had first-hand access to the long-term audiological care of a handful of patients implanted with the ABI outside the US (unpublished data) but followed at our center under a compassionate use exemption. Team audiologists observed that an overall sense of benefit was impacted by the presence or absence of speech, language, and educational services in the patient's local area and by the extent of parental involvement prior to treatment. Further, the number of the electrodes within the array which could be successfully programmed to deliver electrical stimulation also impacted potential benefit. The daunting list of factors impacting benefit necessitated careful selection of inclusion criteria, evaluation instruments, and a team approach to evaluating a candidate for this elective craniotomy. An ABI pre-evaluation may require up to 3 days of assessments by the medical team, audiologists, speech-language pathologist, educational specialist, and a pediatric clinical psychologist.

The study costs were a significant issue for the team, potentially slowing recruitment of families and dampening institutional enthusiasm for the study. Slowing recruitment, because few third-party payers would cover the medical/surgical, audiological, and device costs. Few families have the resources, both financial and personal (e.g., paid time off from work). All enrolled families travel a significant distance for the frequent study visits during the first year. The device manufacturer was supportive of our efforts and agreed to provide the devices to the hospital, in the event that a third-party payer denied coverage.

During IDE development, the National Institutes of Health National Institute on Deafness and Other Communication Disorders (NIH NIDCD) issued a clinical trial program announcement with special review considerations for funding under the U01 cooperative agreement mechanism. The solicitation contained specific provisions for funding Phase I feasibility trials. The grant proposal requirements had some, but not complete, overlap with the requirements for an IDE. The team elected to submit the formal IDE documentation to the FDA and the grant proposal to NIDCD in parallel.

The NIDCD review panel required additional supports for safety/risk mitigation. First, a Data Safety Monitoring Board (DSMB) was necessary, which the FDA did not require for Phase I feasibility study [22]. The DSMB was designed to incorporate surgical, medical, and audiological researchers, along with a statistician with expertise in clinical trials, for oversight.

Second, the NIH review panel noted that predicting lack of cochlear implant benefit in the presence of abnormal inner ear anatomy was not clear-cut (e.g., [23]). The review panel sharpened the benefit/risk discussion, suggesting the inclusion criteria be altered to ensure that cases with ambiguous or unclear imaging data be recommended for a cochlear implant prior to full consideration for an ABI. "Ambiguous imaging" included radiological finding

of a smaller than normal cochlear nerve or cochlea. These imaging indications represented a clinical challenge for choice of treatments and the NIH review panel opted for treatment choices on the conservative side.

The IDE protocol was adapted to conform to both suggestions and the U01 application was resubmitted after the FDA approved the IDE. A short description of the protocol, highlighting the significant safety and clinical issues, is below.

Clinical Trial Protocol: Mitigation of Risk

Inclusion Criteria

Marshalling the appropriate evidence for the feasibility IDE involved a close examination of the scientific literature on the developing brain and critical periods of sensory development, published reports of the surgical challenges in retrosigmoid craniotomies in very young children, radiological findings of inner ear anatomy, and our clinical experience with techniques to determine whether or not a young child perceives sound from the device. The pressing clinical need to provide children with abnormal inner ear anatomy a treatment option and defining potential benefits shaped the team's choices for inclusion criteria, among which were the age range for implantation and development of a comprehensive battery of pre- and post-surgical assessments.

The inclusion criteria were developed around the characteristics of a child most likely to benefit with the fewest surgical risks. The team was aware of the trade-offs between strict inclusion criteria, emphasizing surgical and device safety, and the pace of study enrollment; those criteria consequently limit the pool of potential participants. The inclusion criteria required clear radiographic evidence (CT and MRI) of abnormal inner ear anatomy unlikely to show benefit with a cochlear implant. Bilateral abnormal inner ear anatomy underlying congenital deafness is rare [24], and it is even less common for such a child to be without additional syndromic or cognitive issues. The medical examination included blood tests, vaccinations, and examinations by the neurosurgeon and neurotologist to determine fitness for the surgical procedure.

Surgical safety considerations led to limiting the youngest age to 2 years, to allow sufficient development for neurological surgery. Although pediatric ABI placement may be shown to be safe and beneficial for children as young as 14 months of age [25], 2 years of age allows the child to be of sufficient weight (and therefore blood volume) and adequate cardiopulmonary reserve. The maximum age of 6 years was chosen based on research suggesting that the sensitive period for central auditory development occurs during first 3.5 years of life [26]. Recognizing the sound patterns found in familiar words is mastered by 2 years of age in children with normal hearing [27]. From a perceptual standpoint, children receiving early auditory stimulation with the ABI can be expected to develop auditory skills that are within the range of performance shown for children with cochlear implants [28, 29]. Older candidates, who either had been born with normal hearing and deafened from meningitis or have not benefited from a cochlear implant, may have had some auditory awareness during the critical period. These children might benefit from an ABI, even at an older age than a child with no prior auditory experience.

Finally, a comprehensive assessment of the child and his/her family was important to determine if the environment would be supportive of the long therapeutic process. The process involved becoming familiar with the device, auditory training through pairing electrical stimulation with sound stimuli, and extensive work teaching speech (expressive and receptive skills). The child needed to be cognitively and developmentally normal, as assessed by a pediatric clinical psychologist, who has expertise in assessing deaf/hard of hearing young children. These criteria were directed toward mitigation of device-related adverse events. If the child was unable to communicate using sign language or could not be trained to respond to tactual or auditory stimuli during device programming, the possibility for unknowingly stimulating an electrode near critical life sustaining brainstem centers was increased. Normal cognitive capacity enables the child to quickly learn to appropriately respond if he/she felt an electrical stimulus more like a sound or resulted in discomfort.

The test battery included a full audiological work-up to establish the extent of the child's deafness: pure-tone thresholds (air and bone conduction), auditory brainstem responses, otoacoustic emissions, and acoustic reflexes. These audiological tests are standard of care for a deaf child for whom surgical intervention is contemplated as a treatment. The pre-screening battery required evaluations from a speech-language pathologist and educator of the deaf and hard-of-hearing. These are also standard of care, but in the context of the IDE, results were interpreted with risk mitigation in view.

To advance to surgery, the medical team specified that the child's auditory nerve and/or cochlea clearly met the radiographic criteria of abnormal or absent and that the child was medically able to withstand surgery. If the child had not had a cochlear implant and imaging did not clearly indicate abnormal nerve anatomy, the team would decline to implant the child. The audiologist and pediatric psychologist specified that the child was deaf and the family and child would be able to accommodate the extensive therapeutic process. The speech-language pathologist and educator of the deaf determined the potential of the child to develop auditory/oral communication skills [13, 29, 30].

Endpoints

The primary endpoint was evaluation of two safety outcomes: the number of expected serious surgery-related adverse events and the number of unexpected serious device-related adverse events, which occurred during the 12-month follow-up period. For the ABI to be considered a feasible treatment going forward, the number of serious expected surgical events could not exceed the known rate of retrosigmoid craniotomy events. Retrosigmoid craniotomy carries with it the risk of cerebrospinal fluid leak [31–33], meningitis [34], hematoma [31], facial palsy [35], cerebellar edema and hydrocephalus [36]. Each of these risks, in and of themselves, has well-established treatment protocols and do not increase the benefit/risk tradeoff adversely. The incidence of these adverse events must not be greater than that in the literature.

Feasibility will first turn on medical safety and then be further demonstrated if stimulation of the device did not result in life-threatening NASE. If these basic risks were appropriately minimal, the next step was showing the device is efficacious. A sample size of 10 was not sufficient for dispositive evidence of efficacy, but early efficacy can be shown through

sound detection and good electrical thresholds for the sound frequencies associated with speech sounds (0.25, 0.5, 1, 2, 3, 4 kHz). Sound detection and electrical thresholds supportive of speech awareness were chosen as secondary, preliminary, endpoints. These endpoints were developmentally appropriate for the subjects' age and are not typically used in clinical trials of adults implanted with the ABI [37]. Based on our early experience with three children [28, 29] implanted outside the US, auditory skills such as detection of speech sounds, ability to tell the difference between words with 1 and 2 syllables, and the ability to identify words within a limited number of alternatives were expected.

Follow-up

Finally, the follow-up period was not a straightforward decision. Feasibility studies tend to provide data sooner rather than later, but accommodating to an ABI in a young child takes longer to reveal even preliminary efficacy. The follow-up period was broken into two parts, a year-long closely monitored safety evaluation (every month until 3 months after device activation, then every 3 months), and an additional 2-year period (2 annual evaluations) to evaluate efficacy.

Device-related risks

For device stimulation-related risks, the protocol specified an assessment of device function prior to stimulation in the awake child, and a cautious approach to device programming. The electrically evoked auditory brainstem response (EABR) of the cochlear nucleus assisted the neurosurgeon in determining appropriate placement [38–41]. During electrical stimulation of the device during surgery, the child's heart rate and breathing were monitored by the anesthesiologist and the electrophysiologist watched for any facial stimulation. The EABR procedure is conducted a second time, under light anesthetic, 1 month after surgery. Our experience has shown that the electrode array may shift during the immediate post-surgical period. The anesthesiologist again monitored cardiac and respiratory function and the electrophysiologist monitored facial movement. The information from the two EABR recordings were communicated to the programming audiologist, indicating which electrodes potentially stimulate an auditory neural pathway and electrodes which potentially stimulate non-auditory areas.

During the first electrical stimulation in the awake child, the audiologist, in conjunction with an experienced test assistant, stimulated one electrode at a time, at very low levels, generally starting with those electrodes that produced probable auditory responses during the EABR. During this process, electrodes that elicited a possible NASE were turned off and not included in the overall set of electrodes comprising the device's program for electrical stimulation. Electrodes not included in the program will be unable to receive inadvertent stimulation.

During these initial sessions, the audiologists closely observed the child for any sign that he/she experienced subtle NASE such as eye twitching, eye rubbing, light coughing or touching the throat, touching or holding the head, ear pulling or rubbing, postural sway, or tingling in the arms, legs, or trunk. If less subtle NASE, such as choking or breathing difficulties, were observed, the awaiting PALS team would have been summoned. To date,

we have never observed a serious NASE requiring PALS support. For risk mitigation, during the four initial programming sessions, all electrodes were stimulated, one electrode at a time. Any electrode showing possible NASE was de-activated. It is unlikely that NASE would emerge at a later time on the electrodes selected as usable.

Early Results

The study was approved by the FDA, approved for funding by NIDCD, and the Children's Hospital Los Angeles Institutional Review Board (CCI-13-00384). From study start early in 2014 to date, we have been contacted by 47 families and enrolled 7 candidates (see Table 1). One family elected to not proceed with the surgery; two others did not meet the inclusion criteria. Four were taken to surgery, with a single expected adverse event in the first subject. The adverse event, a cerebrospinal leak post-surgery resolved uneventfully with a lumbar drain. Subsequently, the other 3 surgeries proceeded with a lumbar drain placed during the surgery and no cerebrospinal fluid leak has occurred.

All 4 children were programmed uneventfully, with no serious NASE observed. One child had some postural sway immediately after the electrode array was stimulated, which resolved by the end of the programming session (up to 2 hours later). No other NASE have been observed in the 4 subjects. Three of the 4 children are nearing their 1 year evaluation. Acquisition of auditory skills is progressing for all children; all children have met the preliminary efficacy endpoints.

Conclusions

Until recently, young children who are bilaterally congenitally deaf with abnormal inner ear anatomy did not have a treatment option in the US. Outside of the US, surgeons have implanted an ABI in non-NF2 pediatric patients, with apparent success (no serious side effects and developed the ability to perceive sound). Surgeons and audiologists in the US faced steep regulatory and funding challenges to develop a clinical trial for implanting the ABI in pediatric patients.

Using the mechanisms offered by the FDA, we worked closely with the FDA to secure an approved IDE, first by submitting a sponsor-investigator pre-IDE document. Discussions with the FDA resulted in a substantially improved document, framed as an early feasibility study with 10 subjects. An additional safety measure included a pause in study enrollment after the 5th implantation, allowing for FDA review of all the data. The protocol described procedures for mitigating known surgical risks and known device-related risks. To date, the study has enrolled 7 subjects, 4 of whom have proceeded to implantation. All subjects have begun to show preliminary benefit from device use.

Acknowledgments

This study was funded by grant 7U01DC013031 from the National Institute on Deafness and Communication Disorders. The study is conducted under IDE G120194, University of Southern California. [www.clinicaltrials.gov](https://www.clinicaltrials.gov/ct2/show/study?term=NCT02102256) #NCT02102256.

Los Angeles Pediatric ABI Team

Keck School of Medicine of University of Southern California

Laurie S. Eisenberg, PhD, Co-Principal Investigator

Robert V. Shannon, PhD, Co-Investigator

Laurel M. Fisher, PhD., Co-Investigator

Amy S. Martinez, MA, Research Audiologist, Clinical Coordinator

Margaret Winter, MS, Lead ABI Audiologist

Jamie Glater, AuD, ABI Audiologist

Dianne Hammes-Ganguly, MA, Speech Language Pathologist

Debra Schrader, Educational Liaison

Children's Hospital Los Angeles

Mark Krieger, MD, Chief, Pediatric Neurosurgery

Huntington Medical Research Institutes, House Clinic

Eric P. Wilkinson, MD, Co-Principal Investigator

Marc S. Schwartz, MD, Neurosurgeon

References

1. Sennaroglu L, Ziyal I. Auditory brainstem implantation. *Auris Nasus Larynx*. 2012; 39(5):439–50. [PubMed: 22196501]
2. Roland P, et al. Assessment of cochlear implant candidacy in patients with cochlear nerve deficiency using the P1 CAEP biomarker. *Cochlear Implants Int*. 2012; 13(1):16–25. [PubMed: 22340748]
3. Cunningham M, et al. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics*. 2003; 111(2):436–40. [PubMed: 12563074]
4. Cotichia JM, et al. Characteristics of sensorineural hearing loss in children with inner ear anomalies. *Am J Otolaryngol*. 2006; 27(1):33–8. [PubMed: 16360821]
5. Otto SR, et al. Multichannel auditory brainstem implant: update on performance in 61 patients. *J Neurosurg*. 2002; 96:1063–1071. [PubMed: 12066908]
6. Nevison B, et al. Results from a European Clinical Investigation of the Nucleus® Multichannel Auditory Brainstem Implant. *Ear Hear*. 2002; 23:170–183. [PubMed: 12072610]
7. Colletti V, et al. Auditory brainstem implantation: The University of Verona experience. *Otolaryngology - Head and Neck Surgery*. 2002; 127(1):84–96. [PubMed: 12161736]
8. Colletti V, et al. Hearing habilitation with auditory brainstem implantation in two children with cochlear nerve aplasia. *International Journal of Pediatric Otorhinolaryngology*. 2001; 60:99–111.
9. Colletti V. Auditory outcomes in tumor vs. nontumor patients fitted with auditory brainstem implants. *Adv Otorhinolaryngol*. 2006; 64:167–85. [PubMed: 16891842]
10. Colletti V, et al. Auditory brainstem implant as a salvage treatment after unsuccessful cochlear implantation. *Otol Neurotol*. 2004; 25(4):485–96. discussion 496. [PubMed: 15241227]
11. Tan VY V, D'Souza D, Low WK. Acoustic brainstem implant in a post-meningitis deafened child- Lessons learned. *Int J Pediatr Otorhinolaryngol*. 2012; 76(2):300–2. [PubMed: 22204960]
12. Otto SR, Waring M, Kuchta J. Neural Response Telemetry and Auditory/Non-auditory Sensations in 15 Recipients of Auditory Brainstem Implants. *J Am Acad Audiol*. 2005; 16:219–227. [PubMed: 16050332]
13. Goffi-Gomez MV, et al. Auditory brainstem implant outcomes and MAP parameters: report of experiences in adults and children. *Int J Pediatr Otorhinolaryngol*. 2012; 76(2):257–64. [PubMed: 22226602]
14. Behr R, et al. Consensus Statement of the ABI Advisory Group. *Journal of Laryngology & Otology*. 2000; 114(Suppl 27):2.

15. Sennaroglu L, et al. Auditory Brainstem Implantation in Children and Non-Neurofibromatosis Type 2 Patients: A Consensus Statement. *Otol Neurotol*. 2011; 32:187–191. [PubMed: 21224730]
16. Tysome JR, et al. English consensus protocol evaluating candidacy for auditory brainstem and cochlear implantation in neurofibromatosis type 2. *Otol Neurotol*. 2013; 34(9):1743–7. [PubMed: 24136318]
17. Sennaroglu L, Sennaroglu G, Atay G. Auditory Brainstem Implantation in Children. *Current Otorhinolaryngology Reports*. 2013:1–12.
18. Bowen DJ, et al. How we design feasibility studies. *Am J Prev Med*. 2009; 36(5):452–7. [PubMed: 19362699]
19. Papsin B. Cochlear implantation in children with anomalous cochleovestibular anatomy. *Laryngoscope*. 2005; 115(Jan. Suppl):1–26. [PubMed: 15626926]
20. Buchman C, et al. Cochlear implantation in children with labyrinthine anomalies and cochlear nerve deficiency: implications for auditory brainstem implantation. *Laryngoscope*. 2011; 121(9):1979–88. [PubMed: 22024855]
21. Johnson, KC.; Wiley, S. Cochlear Implantation in Children with Multiple Disabilities. In: Eisenberg, L., editor. *Clinical Management of Children with Cochlear Implants*. Plural Publishing, Inc; San Diego, CA: 2009.
22. FDA. Guidance for industry and Food and Drug Administration staff: Factors to consider when making benefit-risk determinations in medical device premarket approval and de novo classifications. Silver Spring, MD: 2012.
23. Young NM, et al. Pediatric cochlear implantation of children with eighth nerve deficiency. *Int J Pediatr Otorhinolaryngol*. 2012; 76(10):1442–8. [PubMed: 22921779]
24. Kaplan AB, et al. Auditory brainstem implant candidacy in the United States in children 0–17 years old. *International Journal of Pediatric Otorhinolaryngology*. 2015; 79(3):310–315. [PubMed: 25577282]
25. Colletti V, et al. Auditory brainstem implant (ABI): new frontiers in adults and children. *Otolaryngol Head Neck Surg*. 2005; 133(1):126–38. [PubMed: 16025066]
26. Sharma A, et al. Early cochlear implantation in children allows normal development of central auditory pathways. *Ann Otol Rhinol Laryngol Suppl*. 2002; 189:38–41. [PubMed: 12018346]
27. Swingle D, Aslin RN. Spoken word recognition and lexical representation in very young children. *Cognition*. 2000; 76(2):147–66. [PubMed: 10856741]
28. Eisenberg LS, et al. Studies in pediatric hearing loss at the House Research Institute. *J Am Acad Audiol*. 2012; 23(6):412–21. [PubMed: 22668762]
29. Eisenberg LS, et al. Comprehensive Evaluation of a Child With an Auditory Brainstem Implant. *Otology & Neurotology*. 2008; 29:251–257. [PubMed: 18025999]
30. Watkin P, et al. Language ability in children with permanent hearing impairment: the influence of early management and family participation. *Pediatrics*. 2007; 120(3):e694–701. [PubMed: 17766510]
31. Li D, et al. Complications in retrosigmoid cranial nerve surgery. *Acta Otolaryngol*. 2010; 130(2):247–52. [PubMed: 19593681]
32. Schwartz MS, et al. Auditory brainstem implants. *Neurotherapeutics*. 2008; 5(1):128–36. [PubMed: 18164492]
33. Kim JP, et al. Surgical complications of pediatric auditory brain stem implantation in patients with narrow internal auditory canal following retrosigmoid approach. *Childs Nerv Syst*. 2012; 28(6):933–8. [PubMed: 22234544]
34. Colletti V, et al. Complications in Auditory Brainstem Implant Surgery in Adults and Children. *Otology & Neurotology*. 2010; 31:558–564. [PubMed: 20393378]
35. Baroncini M, et al. Retrosigmoid approach for meningiomas of the cerebellopontine angle: results of surgery and place of additional treatments. *Acta Neurochir (Wien)*. 2011; 153(10):1931–40. discussion 1940. [PubMed: 21800106]
36. Teo MK, Eljamel MS. Role of craniotomy repair in reducing postoperative headaches after a retrosigmoid approach. *Neurosurgery*. 2010; 67(5):1286–91. discussion 1291–2. [PubMed: 20871444]

37. FDA. C. CDRH. Leveraging existing clinical data for extrapolation to pediatric uses of medial devices: Draft Guidance. FDA; Rockville, MD: 2015.
38. Nevison B. A guide to the positioning of brainstem implants using intraoperative electrical auditory brainstem responses. *Adv Otorhinolaryngol.* 2006; 64:154–66. [PubMed: 16891841]
39. O'Driscoll M, El-Dereby W, Ramsden R. Brain Stem Responses Evoked by Stimulation of the Mature Cochlear Nucleus With an Auditory Brain Stem Implant. *Ear Hear.* 2011; 32:286–299. [PubMed: 21157353]
40. O'Driscoll M, et al. Brain Stem Responses Evoked by Stimulation With an Auditory Brain Stem Implant in Children With Cochlear Nerve Aplasia or Hypoplasia. *Ear Hear.* 2010; 32:1–13.
41. Waring MD. Intraoperative electrophysiologic monitoring to assist placement of auditory brainstem implant. *Ann Otol Rhinol Laryngol Suppl.* 1995; 166:33–6. [PubMed: 7668693]

Figure 1.
Anatomical placement and schematic of the Nucleus 24 auditory brainstem implant (Cochlear Americas).

Table 1

Subject Characteristics

Subject	Gender, Age	Anatomy	Cochlear Implant	Surgery	Adverse Event
1	M, 3 years	Nerve aplasia	Bilateral	Yes	CSF leak
2	F, 3 years	Nerve aplasia	Unilateral	Yes	None
3	F, 2 years, 3 months	Nerve aplasia	Unilateral	Yes	None
4	F, 4 years, 5 months	Absent cochleas	No	No	N/A
5	M, 4 years, 11 months	Absent cochleas	No	Yes	None
6	F, 2 years, 4 months	Nerve deficiency	Bilateral	No	N/A
7	M, 2 years, 11 months	Cochlear malformation	Bilateral	No	N/A