Outcomes in Children with Cochlear Implants and Pre-Operative Residual Hearing: Electric Only and Electric-Acoustic Stimulation

IRB: 17-2360
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Protocol Number: 1.7

Principal Investigator: Lisa Park, AuD

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
All	Incorporated UNC Team Edits	
All	Incorporated suggestions from Scientific Review Committee	
1, 3, 6, 8, 9, 11, 12	Substituting the children's SSQ for the Peds- QL	The Peds-QL is proving to be an inconsistent QOL measure in another ongoing study. The pediatric version of the SSQ is proving to provide much more data.
1, 3, 6	Testing in hearing aid (HA) condition rather than CI alone in Arm 1 participants	This will allow us to compare to pre-operative scores and account for developmental aspects. In addition, the CI alone condition would be novel and unfamiliar in this group, likely making for an invalid measurement. We can instead use the Arm 2 participants for comparison as they will have been used to a full CI program.

5	**Changing inclusion criteria to include 5-year-olds and children with a composite language score down to 60.**	**Effort to ease recruitment. Five-year-olds with residual hearing are capable of completing the test protocol. Many potential candidates have language skills that are poorer than we expected, and we want to be able to include these children and measure changes in language abilities as well. A standard score of 60 would avoid floor effects and still include children who are able to complete the test protocol.**
5	**Specifying that a neurotologist will read scans of potential candidates under a waiver of HIPAA to confirm a lack of cochlear nerve deficiency.**	**This change is in response to the withdrawal of a subject who was noted to have CND after enrolment.**
1, 2, 6	**Adding SONNET 2 EAS as a device. Removing Maestro 7 as a device and simply including the Maestro System.**	**SONNET 2 EAS has been FDA approved and will be arriving in patient kits. It is an updated version of the SONNET EAS device. Maestro 7 is no longer considered experimental and we will be using the FDA approved versions of the software from this point on as they now provide what we need to fit the EAS devices.**
1, 5, 6	**Removing Leiter-R from protocol and changing exclusion criteria to read "known or suspected cognitive impairment."**	**The Leiter-R has proven to be an unnecessary and cumbersome measure. For safety measures in light of COVID-19 it is being removed as a screening tool.**
5	**Changing screening procedures**	**To ease scheduling difficulties in light of COVID-19, investigators may reach out to potential candidates prior to initial stimulation to discuss the study and schedule initial stimulation visits appropriately.**

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational Device Exemption (IDE) sponsor (if applicable), funding agency, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

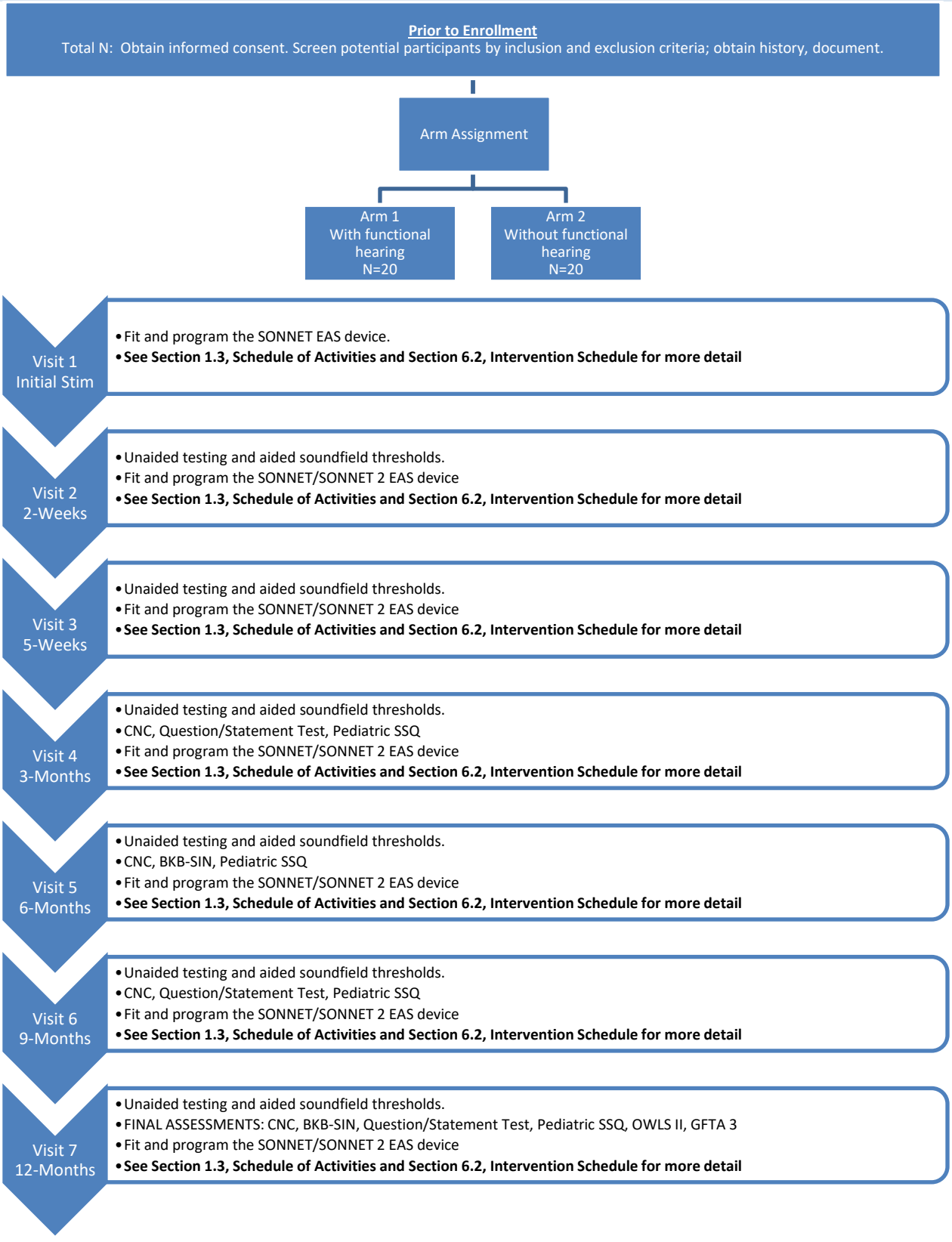
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Outcomes in Children with Cochlear Implants and Pre-Operative Residual Hearing: Electric Only and Electric-Acoustic Stimulation.
Study Description:	The Children's Cochlear Implant Center at UNC has seen evidence of postoperative hearing preservation in pediatric cochlear implant (CI) recipients during routine clinical care and data from pilot studies. The primary aim of this study is to investigate speech perception performance in pediatric CI recipients with functional pre-operative hearing.
Objectives:	*Primary Objective:* To determine if listening with electric-acoustic stimulation (EAS) provides improved speech understanding over listening with the CI alone (CI-alone) in pediatric CI recipients.
	Secondary Objectives: 1. To compare the pre-operative speech perception and quality of life scores with traditional hearing aids to post-operative scores listening with a CI alone in children with pre-operative low frequency hearing.
	2. To determine if listening with EAS achieves better performance and/or subjective benefit as compared to pre-operative findings with conventional amplification.
	3. To evaluate the differences in identification of questions vs answers in children listening to EAS vs CI-alone programs.
Endpoints:	*Primary Endpoints*: 1. Mean CNC word scores, comparing EAS and CI-alone conditions at 12 months post stimulation.
	2. Mean BKB-SIN scores, comparing EAS and CI-alone conditions at 12 months post stimulation.

	Secondary Endpoints: 1. Mean Pediatric SSQ scores, comparing Pre-operative and 12 month post stimulation scores in both groups.
	2. Mean CNC word scores, comparing Pre-operative and best listening conditions at 12 months post stimulation in both groups.
	3. Mean articulation, expressive, and receptive language scores, comparing pre-operative scores to the 12 month test point for both groups using the Goldman Fristoe Test of Articulation 3 (GFTA 3) and the Oral and Written Language Scales II (OWLS II).
	4. Mean Question/Answer Task scores, comparing EAS to CI-Alone conditions at the 12 month test point.
Study Population:	Two cohorts of CI recipients aged 6 through 17 years who had pre-operative low frequency residual hearing. Subjects in Arm 1 will present with a post-operative low frequency pure tone average (125, 250, and 500 Hz) of $\leq$ 75 dB HL, and those in Arm 2 will present with a post-operative low frequency pure tone average (LFPTA) that exceeds 75 dB HL.
Phase:	NA
Description of Sites/Facilities Enrolling Participants:	Subjects will be seen and enrolled at The University of North Carolina at Chapel Hill. Physical locations include The Children's Cochlear Implant Center at UNC and the Carolina Crossing satellite clinic.
Description of Study Intervention:	The MED-EL EAS System is capable of providing electric stimulation to the mid- to high-frequency region of the cochlea and acoustic amplification to the low frequency regions for candidates with residual low frequency hearing sensitivity. The combination of acoustic (hearing aid) and electrical stimulation to the same ear is made possible through the external SONNET/SONNET 2 EAS Processor working in conjunction with the internal CI. Patients without residual acoustic hearing can use the SONNET/SONNET 2 EAS Processor to provide electric stimulation; in these cases the patient does not wear the hearing aid component. The SONNET/SONNET 2 EAS Audio Processor is programmed with the MED-EL MAESTRO System Software used as part of typical clinical care.
Study Duration:	48 months
Participant Duration:	12 months

1.2 SCHEMA


Prior to Enrollment
Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Arm Assignment
Arm 1
With functional hearing
N=20
Arm 2
Without functional hearing
N=20
Visit 1
Initial Stim
• Fit and program the SONNET EAS device.
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail
Visit 2
2-Weeks
• Unaided testing and aided soundfield thresholds.
• Fit and program the SONNET/SONNET 2 EAS device
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail
Visit 3
5-Weeks
• Unaided testing and aided soundfield thresholds.
• Fit and program the SONNET/SONNET 2 EAS device
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail
Visit 4
3-Months
• Unaided testing and aided soundfield thresholds.
• CNC, Question/Statement Test, Pediatric SSQ
• Fit and program the SONNET/SONNET 2 EAS device
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail
Visit 5
6-Months
• Unaided testing and aided soundfield thresholds.
• CNC, BKB-SIN, Pediatric SSQ
• Fit and program the SONNET/SONNET 2 EAS device
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail
Visit 6
9-Months
• Unaided testing and aided soundfield thresholds.
• CNC, Question/Statement Test, Pediatric SSQ
• Fit and program the SONNET/SONNET 2 EAS device
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail
Visit 7
12-Months
• Unaided testing and aided soundfield thresholds.
• FINAL ASSESSMENTS: CNC, BKB-SIN, Question/Statement Test, Pediatric SSQ, OWLS II, GFTA 3
• Fit and program the SONNET/SONNET 2 EAS device
• See Section 1.3, Schedule of Activities and Section 6.2, Intervention Schedule for more detail

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/ Enrollment & Initial Stim: Day 1	Study Visit 2 Day 14 +/-5 days	Study Visit 3 Day 35 +/- 8 days	Study Visit 4 Day 90 +/-14 days	Study Visit 5 Day 180 +/-14 days	Study Visit 6 Day 270 +/-14 days	Final Study Visit 7 Day 365 +/-14 day
Informed consent	X						
Review of Demographics	X						
Review of Hearing History	X						
Review of Pre-Op Speech and Language Testing	X						
Unaided Testing	X	X	X	X	X	X	X
Pediatric SSQ	X			X	X	X	X
Arm Assignment	X						
Speech Processor Programming		X	X	X	X	X	X
Soundfield Thresholds		X	X	X	X	X	X
CNC Word List				X	X	X	X
Question/Answer Test				X		X	X
BKB-SIN					X		X
OWLS II							X
GFTA 3							X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

As CI candidacy continues to expand, The Children's Cochlear Implant Center at UNC has seen evidence of postoperative hearing preservation in pediatric CI recipients during routine clinical care and data from pilot studies. Currently, only one manufacturer, Cochlear Americas, offers an FDA approved speech processor that allows us to take advantage of this functional hearing and use it to provide additional temporal cues. This external speech processor only works with internal devices from Cochlear Americas. MED-EL also has an approved speech processor, but it is currently only labeled for adult use, despite its more pediatric friendly design. The Cochlear Americas external speech processor requires use of a Receiver in the Canal (RIC) which is easy for children to damage and does not fit in smaller ears. The MED-EL SONNET/SONNET 2 EAS speech processor uses a standard tone-hook and earmold just like a behind-the-ear hearing aid. An earmold can be made to fit many shapes and sizes of ear canals, and it is made from vinyl or silicone so it is comfortable.

The primary aim of this study is to investigate speech perception performance with EAS in pediatric CI recipients with postoperative hearing preservation. While hearing preservation rates are good in our clinic, they are not guaranteed. Children with progressive hearing loss may continue to lose hearing, even if they maintain some residual hearing immediately after surgery. As a secondary aim, we intend to investigate outcomes in children who do not maintain residual hearing and are fit with traditional CI programming methods. Children with more residual hearing are being implanted, and this study design allows us to validate outcomes in both populations.

2.2 BACKGROUND

Low-frequency acoustic hearing provides better temporal and spectral cues than low-frequency electrical stimulation (Dunn et al, 2010; Gifford et al, 2010; Incerti et al, 2013). These are cues that allow for localization, music appreciation, hearing in noise, and prosodic recognition. Preservation of residual hearing is of continuing clinical interest in cochlear implantation (Adunka et al, 2013; Adunka, Pillsbury, & Buchman, 2010; Carlson et al, 2011; Havenith et al, 2014; Santa Maria, Gluth, Yuan, Atlas, & Blevins, 2014; Van Avel et al, 2015). Modified electrode arrays and surgical techniques have resulted in postoperative hearing preservation (Adunka et al, 2014; Adunka, Pillsbury, & Buchman, 2010; Anagiotos et al 2015; Carlson et al, 2011; Frixon, Kobler, & Rask-Anderson, 2012; Havenith et al, 2013; Kisser et al, 2016; Santa Maria et al, 2013; Santa Maria et al, 2014; Skarzynski et al, 2014; Sweeney et al, 2016; Tamir et al, 2012; Yao, Turner & Gantz, 2006). When low-frequency hearing is preserved, there is an opportunity to provide high frequency hearing through electric stimulation and low-frequency cues through acoustic hearing.

Research with adult CI recipients has shown improved listening skills in quiet and noise when combining acoustic and CI technology, known as electric-acoustic stimulation (EAS), over fully acoustic or electric stimulation (Adunka, et al, 2013; Dillon, et al, 2014; Gfeller, et al, 2007; Gifford, et al, 2013; Gifford, Dorman, & Brown, 2010; Helbig & Baumann, 2010; Incerti, Ching, & Cowan, 2014; Roland, et al, 2015; Sheffield, Jahn, & Gifford, 2015). In EAS modes of hearing, frequencies with residual hearing in the implant ear are amplified using acoustic technology, and frequencies that cannot be sufficiently amplified are stimulated through traditional CI technology. There are now commercially available external speech processors that combine these two technologies in one device.

CI users are known to have poor spectral resolution due to limited neural survival rates and limitations of electrical stimulation. The addition of acoustic stimulation is thought to increase spectral resolution, thereby improving speech understanding, particularly in noise (Gifford & Dorman, 2012).

As of yet, there are few peer reviewed studies that investigate EAS in the pediatric population and all reports are on small groups of children. Wolfe, et al (2017) report on a cohort of 7 children aged 6-16 who were fit with EAS speech processors and evaluated in quiet and in noise. In this small study, subjects were found to benefit from EAS in noise and in quiet when compared to electric or acoustic only conditions. The children in this study had been wearing electric stimulation only for at least 6 months before being fit with the EAS speech processor. In the second study, Scholz et al (2017) also report on a small group of 6 children (9 ears) aged 6-10 years who had worn full electric programs for an average of 5.9 years before being fit with EAS processors. Contrary to Wolfe et al, no significant difference was found between the EAS and electric conditions. Skarzynski et al (2007) present on 6 children, some of whom had CI-alone experience and some who did not. An improvement in speech perception was noted over preoperative scores. Skarzynski and Lorens (2010) again show benefit of EAS in children over traditional hearing aids, but neither of these papers compare EAS outcomes to CI-alone listening. No peer reviewed studies exist that investigate the use of EAS in children when they are fit with the device from initial stimulation.

In reviewing our patient database, 81% of children who had stable hearing thresholds pre-operatively and a LFPTA of 65 dB or better maintained functional hearing for more than a year after surgery (n=17/21). Of those patients, 100% of patients implanted with the MED-EL SYNCHRONY Cochlear Implant with FLEX24 electrode array had residual hearing at 12 months post-op. Across all patients included in this review, the mean change in LFPTA was 14 dB HL. For children with progressive hearing loss pre-operatively, only 36% had functional hearing more than a year after surgery (n=18/50). The mean change in this group was 36 dB HL; not surprising given the already progressive nature of the loss.

A pilot study completed with 16 children using the Cochlear Americas device indicated that EAS was superior to traditional CI programs for children with residual hearing. CNC word scores were significantly better ($p<0.001$) for EAS programs (Mean=63.50%) than CI alone (Mean=44.63%). This held true for sentences in noise as well ($P<0.001$) with a mean EAS score of 70.74% and a mean CI alone score of 53.94%. For children who were recently implanted, we were able to compare outcomes to pre-operative scores. CNC word scores with a hearing aid (M=26.25%) were poorer than those in a CI-alone condition (Mean=38.00%), but this did not reach statistical significance. The EAS Condition (Mean=63.00%) was significantly higher than both the pre-operative hearing aid condition ($p<0.01$) and the CI alone condition ($p<0.01$). There may have been learning effects as the subjects were typically tested acutely in the CI-alone condition. We did not look at outcomes in children who lost residual hearing in this pilot group, but according to our database, children who had preoperative residual hearing and do not have enough hearing to be fit with EAS technology have an average CNC word score of 61.76%. The pre-operative CNC scores in this group are similar to the pilot group (M=25.21%) This leads us to believe that our pilot data may have been impacted by learning effects and we feel it is prudent to include the loss of hearing group that would be adapted to the CI-alone condition before testing.

The Children's Cochlear Implant Center at UNC offers three different device manufacturers for children who are receiving a cochlear implant and have sufficient acoustic hearing to confer a functional benefit. The decision on which device to implant is left up to the family, unless the surgeon has a preference based on anatomy. Families choosing MED-EL will receive the same internal and external device

regardless of whether or not they choose to participate in the study. The SYNCHRONY Implant is not experimental. The SONNET/SONNET 2 EAS processor (external hardware) is considered experimental in children. Following implantation, we will approach families of children implanted with the MED-EL device for inclusion in the current study.

All potential subjects in this study will have residual hearing prior to implantation. Participants will be enrolled following surgery in two Arms. The first Arm will be for those subjects who have enough residual hearing to fit with an EAS method. For the purposes of this study, we are defining functional hearing as a LFPTA of 75 dB HL or lower. Arm 2 will be for those who do not have enough residual hearing to amplify following implantation. These patients will be fitted with the same hardware as those in Arm 1, with the exception that they will not wear the hearing aid (HA) component. Having two arms will allow us to compare groups with similar pre-operative hearing and investigate differences in listening in full electric and EAS conditions. Subjects in Arm 1 will be tested in HA-alone and EAS conditions as we anticipate good hearing preservation in this study. Subjects in Arm 2 will be tested in the CI-alone condition. Although unanticipated, it is possible that a subject with residual hearing would be enrolled in Arm 1 and subsequently lose hearing; in these cases they would be removed from Arm 1 and reassigned to Arm 2.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks include (but are not limited to):

- Poor sound quality from the device
- Poorer speech perception and/or quality of life with the CI-alone and/or EAS
- Embarrassment with device use due to device visibility to others
- Loss of residual hearing in the implanted ear
- Pain and/or discomfort from the fit of the earmold and/or the placement of the audio processor and/or coil/magnet
- Facial stimulation from device use
- Dizziness from CI use
- Tinnitus
- External equipment malfunction due to intermittencies in the device (i.e. cable needing to be replaced)

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits include (but are not limited to):

- Improved speech perception in quiet
- Improved speech perception in noise
- Improved quality of life

2.3.3 ASSESSMENT OF POTENTIAL RISKS

- Poor sound quality from the device
    - All of the co-investigators are licensed audiologists with significant experience fitting EAS devices on children. Best practices will be followed to optimize sound quality. Subject feedback will be taken into account during programming.
- Poorer speech perception and/or quality of life with the CI-alone and/or EAS
    - Should a subject find that their speech understanding or quality of life is poorer with the device, they are welcome to withdraw from the study at any time.
    - The SONNET/SONNET 2 EAS processor can be programmed in a traditional manner with no acoustic stimulation.
    - Poorer speech perception or quality of life was not noted during the pilot study for any subject.
- Embarrassment with device use due to device visibility to others
    - Every effort will be made to mitigate cosmetic concerns.
    - There are a variety of earmold possibilities that are less conspicuous and will be presented to subjects.
    - This risk is highly unlikely as potential subjects will have been wearing hearing aids up until the time of cochlear implantation.
- Loss of residual hearing in the implanted ear
    - This is a known risk to cochlear implantation and not increased with the EAS device.
    - Those with progressive hearing loss may have a continuation of that course and lose hearing over the course of the study.
- Pain and/or discomfort from the fit of the earmold and/or the placement of the audio processor and/or coil/magnet
    - There are a variety of earmolds and magnet strengths that can be used to reduce or eliminate pain/discomfort.
    - Every effort will be made to reduce discomfort through alternate fitting methods (headbands, moleskin, etc).
- Facial stimulation from device use
    - This is a known risk to cochlear implantation and not related to the EAS device itself.
    - Facial stimulation can typically be eliminated with proper programming.
- Dizziness from CI use
    - This is a known risk to cochlear implantation and not related to the EAS device itself.
    - Dizziness can typically be eliminated with programming.
- External equipment malfunction due to intermittencies in the device (i.e. cable needing to be replaced)
    - Subjects will be counseled extensively on how to troubleshoot equipment.
    - All subjects receive two speech processors at the time of implantation, ensuring that they have backup equipment and can have access to sound at all times.

- Subjects can always contact the manufacturer or clinicians for assistance with troubleshooting.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. To determine if listening with electric-acoustic stimulation (EAS) provides improved speech understanding over listening with the CI alone (CI-alone) in pediatric CI recipients.	1. Mean CNC word scores, comparing EAS and CI-alone conditions at 12 months post stimulation (Arm 1 to Arm 2). 2. Mean BKB-SIN scores, comparing EAS and CI-alone conditions at 12 months post stimulation (Arm 1 to Arm 2).	The CNC word list is established as a standard test of speech perception outcomes. The BKB-SIN evaluates speech perception in multi-talker babble. Testing in multi-talker babble is an effective way to evaluate differences in listening conditions with and without acoustic stimulation. Both of these tests are routinely given pre-operatively as part of candidacy determination. We will obtain and use these pre-operative scores in our analysis.
Secondary		
1. To compare the pre-operative speech perception and quality of life scores with traditional hearing aids to post-operative scores listening with a CI alone in children with pre-operative low frequency hearing. 2. To determine if listening with EAS achieves better performance and/or subjective benefit as compared to pre-operative findings with conventional amplification	1. Mean Pediatric SSQ scores, comparing Pre-operative and 12 month post stimulation scores in both groups. 2. Mean CNC word scores, comparing Pre-operative and best listening conditions at 12 months post stimulation in both groups. 3. Mean articulation, expressive, and receptive language scores, comparing pre-operative scores to the 12 month test point for both groups using the Goldman Fristoe Test of Articulation 3 (GFTA 3) and the Oral and Written Language Scales II (OWLS II).	The Pediatric SSQ measures perception of speech, spatial, and sound quality outcomes. The language is simple for children with hearing loss to understand. The OWLS II is a test of receptive and expressive language. The GFTA 3 is a test of articulation. Both are given routinely pre-and post-operatively in the clinic for all children

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		who receive CIs. We will obtain and use these pre-operative scores in our analysis.
3. To evaluate the differences in identification of questions vs answers in children listening to EAS vs CI-alone programs.	1. Mean Question/Answer Task scores, comparing EAS to CI-Alone conditions at the 12 month test point (Arm 1 to Arm 2).	The Question/Answer Task (Peng et al, 2012) evaluates a listener's ability to identify statements vs questions using listening alone. We expect that the prosodic differences in these sentences would be more available to those using EAS programs. This would have implications for language development.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Randomization:

This is a non-randomized trial. Participants will fall into one of two arms:

- Arm1. Subjects who receive a CI and present with a post-operative LFPTA of $\leq$ 75 dB HL.
- Arm 2. Subjects with pre-operative low frequency hearing who receive a CI and present with a post-operative LFPTA of > 75 dB HL.

Hypotheses:

1. Subjects will experience an improvement in speech perception in quiet, speech understanding in noise, and identification of prosodic features when listening with EAS as compared to listening to the CI-alone.
2. Subjects will experience an improvement in speech perception in quiet, speech understanding in noise, articulation, language, and quality of life after 12 months of implant use as compared to pre-operative findings with conventional amplification.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Randomization for this study would be inappropriate. Using two arms allows us to examine two groups of subjects with comparable pre-operative characteristics and post-operative characteristics that necessitate different treatment options. For each group, we are able to use a within-subjects design to compare interventions.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

ARM 1

- Children between the ages of 5 and 17 years of age.
- Spoken English as the primary language (speech perception testing conducted in English).
- Recipient of a MED-EL SYNCHRONY Cochlear Implant device.
- Pre-operative LFPTA of $\leq$ 75 dB HL.
- Post-operative LFPTA of $\leq$ 75 dB HL.
- Willing and able to participate in study procedures.
- Realistic parental/patient expectations.
- Composite language standard score of $\geq$60 per the OWLS II as measured within the 6 months prior to enrollment.

ARM 2

- Children between the ages of 5 and 17 years of age.
- Spoken English as the primary language.
- Recipient of a MED-EL SYNCHRONY Cochlear Implant device.
- Pre-operative LFPTA of $\leq$ 75 dB HL.
- Post-operative LFPTA of > 75 dB HL.
- Willing and able to participate in study procedures.
- Realistic parental/patient expectations.
- Composite language standard score of $\geq$60 per the OWLS II as measured within the 6 months prior to enrollment.

5.2 EXCLUSION CRITERIA

- Inability to perform open set speech perception due to oral motor delays.
- Inability to perform test battery due to behavior.
- Suspected or known cognitive impairment.
- Unwilling or unable to participate in study procedures.
- Cochlear nerve deficiency based on a neurotologist's read of imaging.
- Anatomical considerations that necessitated surgical modifications such as ossification, incomplete insertion, or placement in scala vestibuli.

Potential subjects will not be excluded based on race, gender, or ethnicity, although subjects will be excluded if English is not the child's primary language. The test materials in this study are presented in English.

5.3 LIFESTYLE CONSIDERATIONS

There will be no lifestyle restrictions during the course of this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of oral motor delays or behavioral concerns may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential subjects will be identified during the evaluation process for cochlear implantation at the Children's Cochlear Implant Center at UNC. Potential candidates may be recruited by research and/or clinical audiologists on the CI team and/or their implanting physician. Only those who have chosen a MED-EL device will be approached for inclusion.

To offset the time and travel commitment for participation, MED-EL Corporation will provide earmolds and subject compensation cards during the course of the study. The SONNET/SONNET 2 EAS devices themselves are provided as part of the internal device package prior to enrollment.

We anticipate enrollment of 20 subjects in Arm 1 and 20 subjects in Arm 2 (total: 40 subjects).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION DESCRIPTION

The MED-EL EAS System is intended to provide electric stimulation to the mid- to high-frequency region of the cochlea and acoustic amplification to the low frequency regions for candidates with residual low frequency hearing sensitivity. The combination of acoustic (hearing aid) and electrical stimulation to the same ear is made possible through the external SONNET/SONNET 2 EAS Processor working in conjunction with the internal CI.

The MED-EL EAS System is not currently approved or cleared by the FDA for use in the pediatric population. It is limited to investigational use for the purposes of this study. All subjects will be fit with the SONNET/SONNET 2 EAS external audio processor. It is provided as part of the overall device kit prior to enrollment. There is an option to fit with or without the acoustic output. Subjects in Arm 1 with be fit with the acoustic output and a traditional earmold. Those in Arm 2 will be fit without the acoustic output.

6.1.1 SONNET EAS AUDIO PROCESSOR

6.1.1.1 WEIGHT

11.3 g (including batteries)

6.1.1.2 POWER SUPPLY

2 hearing aid batteries type 675 zinc air (1.4 V), high power batteries recommended

6.1.1.3 HARDWARE

- Fully digital signal processing
- 4 Programs
- Up to 12 band pass filters; filter characteristics programmable
- Non-linear amplification programmable
- 2 omnidirectional microphones
- Integrated telecoil
- Audio processor self-test: checksum on programs, continuous parity check
- Automatic Gain Control (AGC) configurable
- FineTuner commands can selectively be disabled
- Acoustic stimulation up to 2000 Hz
- Fully digital hearing aid signal processing
- Independent compressors in up to 7 frequency bands

6.1.1.4 AUDIO INPUT

- Via FM Battery Pack Cover
- Hearing aid type three pin connection (Euro Audio) acc. to IEC 60118–12
- Sensitivity: –57.5 dBV
- Impedance: 4.5 kΩ

6.1.1.5 CONTROLS/INDICATORS

- ON/OFF switch
- Indicator light: 1 multi-color LED

6.1.1.6 MATERIALS

- Mixture of polycarbonate and acrylonitrile-butadiene-styrol polymer (PC/ABS): audio processor
- Polyamide (PA): earhook

6.1.1.7 TEMPERATURE AND HUMIDITY RANGE

- Operating temperature range: 0 °C to 50 °C
- Storage temperature range: –20 °C to 60 °C
- Relative humidity range: 10 % to 93 %

6.1.1.8 RADIO FREQUENCY (RF) LINK (FINETUNER)

Frequency band of reception: 9.07 kHz (±3 %)

6.1.2 CURRENT LABELING

6.1.2.1 INTENDED USE AND INDICATIONS

The user of a SONNET does not need any special skills or elevated level of education, however, the user (or custodian if the user is a child or a handicapped person not able to perform the actions listed below) shall at minimum be able to perform the following actions:

- Switching ON/OFF
- Changing batteries
- Placing/removing SONNET on/from the ear
- Placing/removing coil over/from the implant site

As the SONNET is a component of the MED-EL Cochlear Implant System, all indications stated for the MED-EL Cochlear Implant System are applicable.

To obtain optimal benefit from the CI, candidates and their families shall be sufficiently motivated and shall understand the importance of returning to the CI center for regular processor programming, assessment sessions and training.

6.1.2.2 CONTRA-INDICATIONS

A patient must not receive a SONNET if the individual is known to be intolerant of the materials used in the SONNET. Combined EAS is contra-indicated for patients unable to use acoustic amplification.

The SONNET and any external wireless device (e.g. FineTuner) are not intended to be used in environments where RF transmissions are prohibited (e.g. operating theatre).

As the SONNET is a component of the MED-EL Cochlear Implant System, all contra-indications stated for the MED-EL Cochlear Implant System are applicable.

6.1.3 SONNET 2 EAS AUDIO PROCESSOR

6.1.3.1 WEIGHT

11.0 g (including batteries)

6.1.3.2 POWER SUPPLY

2 hearing aid batteries type 675 zinc air (1.4 V), high power batteries recommended

6.1.3.3 HARDWARE

- Fully digital signal processing
- Various parameters programmable
- 4 Programs selectable
- Up to 12 band pass filters; filter characteristics programmable
- Non-linear amplification programmable
- 2 omnidirectional microphones
- Integrated telecoil
- Audio processor self-test: checksum on programs, continuous parity check
- Automatic Gain Control (AGC) configurable
- FineTuner commands can selectively be disabled
- Acoustic stimulation up to 2000 Hz
- Fully digital hearing aid signal processing
- Independent compressors in up to 7 frequency bands

6.1.3.4 AUDIO INPUT

- Via FM Battery Pack Cover
- Hearing aid type three pin connection (Euro Audio) acc. to IEC 60118–12
- Sensitivity: –57.5 dBV
- Impedance: 4.5 kΩ

6.1.3.5 CONTROLS/INDICATORS

- ON/OFF switch
- Indicator light: 1 multi-color LED

6.1.3.6 MATERIALS

- Mixture of polycarbonate and acrylonitrile-butadiene-styrol polymer (PC/ABS): audio processor
- Polyamide (PA): earhook

6.1.3.7 TEMPERATURE AND HUMIDITY RANGE

- Operating temperature range: 0 °C to 50 °C
- Storage temperature range: –25 °C to 60 °C
- Relative humidity range: 10 % to 93 %
- Atmospheric pressure range: 700hPa (mbar) to 1060 hPa (mbar)

6.1.3.8 RADIO FREQUENCY (RF) LINK (FINETUNER)

Frequency band of reception: 9.07 kHz (±3 %)

6.1.3.9 RADIO FREQUENCY (2.4 GHZ WIRELESS TECHNOLOGY)

- Frequency band of reception/transmission: 2400 MHz – 2483.5 MHz
- Short Range Device (SRD) according to ERC/REC 70-03 Annex 1 (band 1) and Annex 3 (band B)
- Type of Modulation: Gaussian frequency shift keying (GFSK)
- Maximum effective radiated power (ERP): 610µW (-2.15 dBm)
- Channel band width: 2MHz (MED-EL proprietary protocol)
- Channel bandwidth: 1MHz (Bluetooth)

6.1.4 CURRENT LABELING

6.1.4.1 INTENDED USE AND INDICATIONS

The user of a SONNET 2 does not need any special skills or elevated level of education, however, the user (or custodian if the user is a child or a handicapped person not able to perform the actions listed below) shall at minimum be able to perform the following actions:

- Switching ON/OFF
- Changing batteries
- Placing/removing SONNET 2 on/from the ear
- Placing/removing coil over/from the implant site

As the SONNET 2 is a component of the MED-EL Cochlear Implant System, all indications stated for the MED-EL Cochlear Implant System are applicable.

6.1.4.2 CONTRA-INDICATIONS

A patient must not receive a SONNET 2 if the individual is known to be intolerant of the materials used in the SONNET 2. Combined EAS is contra-indicated for patients unable to use acoustic amplification.

The SONNET 2 and any external wireless device (e.g. FineTuner) are not intended to be used in environments where RF transmissions are prohibited (e.g. operating room).

As the SONNET 2 is a component of the MED-EL Cochlear Implant System, all contra-indications stated for the MED-EL Cochlear Implant System are applicable.

6.2 INTERVENTION SCHEDULE

6.2.1 SCREENING

Recipients of the MED-EL SYNCHRONY Cochlear Implant with a pre-operative LFPTA of $\leq$ 75 dB HL will be screened for possible candidacy at initial activation of the external audio processor.

- Complete the consenting process
- Review of preoperative speech and language results for eligibility
- Review of inclusion/exclusion criteria
- Pure tone unaided thresholds in both ears, including 125 Hz
    - Assignment to Arm 1 versus Arm 2 based on hearing levels

6.2.2 INITIAL STIMULATION (COMPLETED ON THE SAME DAY AS SCREENING)

6.2.2.1 TESTING

- Screening for eligibility (see above)
- Complete the Pediatric SSQ Scale

6.2.2.2 FITTING

- Arm 1
    - Obtain RECD values and use them to fit to DSL targets through 70 dB HL audiometric threshold (crossover frequency).
    - Set the most apical electrode frequency boundary for 100 Hz lower than the crossover frequency.
        - Deviations to frequency boundaries may be allowed based on clinical experience and subject performance.
    - Programming using our standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4).
    - Obtain earmold impression.

        - We will use the earmold from the hearing aids worn preoperatively for fitting at initial stimulation.
- Arm 2
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4, default frequency boundaries).

6.2.3 2-WEEK

6.2.3.1 TESTING

- Unaided pure tone thresholds in the implanted ear, including 125 Hz.
- Soundfield thresholds, measured using warble tones, with the SONNET/SONNET 2 EAS
    - Contralateral ear plugged and masked if necessary

6.2.3.2 FITTING

- Arm 1
    - Fit to DSL targets through 70 dB HL audiometric threshold (crossover frequency) using measured RECDs.
    - Set the most apical electrode frequency boundary for 100 Hz lower than the crossover frequency.
        - Deviations to frequency boundaries may be allowed based on clinical experience and subject performance.
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4)
- Arm 2
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4, default frequency boundaries)

6.2.4 5-WEEK

6.2.4.1 TESTING

- Unaided pure tone thresholds in both ears, including 125 Hz.
- Soundfield thresholds, measured using warble tones, with the SONNET/SONNET 2 EAS
    - Contralateral ear plugged and masked if necessary

6.2.4.2 FITTING

- Arm 1
    - Fit to DSL targets through 70 dB HL audiometric threshold (crossover frequency) using measured RECDs.

    - Set the most apical electrode frequency boundary for 100 Hz lower than the crossover frequency.
        - Deviations to frequency boundaries may be allowed based on clinical experience and subject performance.
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4)
- Arm 2
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4, default frequency boundaries)

6.2.5 3-MONTH

6.2.5.1 TESTING – TEST ORDER AND WORD LISTS RANDOMIZED

- Unaided pure tone thresholds in both ears, including 125 Hz.
- Soundfield thresholds, measured using warble tones, with the SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary).
    - Arm 1 participants will be tested in their EAS Map
    - Arm 2 participants will be tested in their familiar, CI-alone map.
- Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, EAS Map (Arm 1) or familiar, CI-alone map (Arm 2)
    - CNC Words
    - Question/Statement Test (Peng et al, 2012)
- Arm 1 only: Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, HA portion only.
    - CNC Words
    - Question/Statement Test
- Pediatric SSQ

6.2.5.2 FITTING

- Arm 1
    - Fit to DSL targets through 70 dB HL audiometric threshold (crossover frequency) using measured RECDs.
    - Set the most apical electrode frequency boundary for 100 Hz lower than the crossover frequency.
        - Deviations to frequency boundaries may be allowed based on clinical experience and subject performance.
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4)
- Arm 2

- Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4, default frequency boundaries)

6.2.6 6-MONTH

6.2.6.1 TESTING – TEST ORDER AND WORD LISTS RANDOMIZED

- Unaided pure tone thresholds in both ears, including 125 Hz.
- Soundfield thresholds, measured using warble tones, with the SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary).
  - Arm 1 participants will be tested in their EAS Map
  - Arm 2 participants will be tested in a familiar, CI-alone map.
- Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, EAS Map (Arm 1) or familiar, CI-alone map (Arm 2)
  - CNC Words
  - BKB-SIN
- Arm 1 only: Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, HA portion only.
  - CNC Words
  - BKB-SIN
- Pediatric SSQ

6.2.6.2 FITTING

- Arm 1
  - Fit to DSL targets through 70 dB HL audiometric threshold (crossover frequency) using measured RECDs.
  - Set the most apical electrode frequency boundary for 100 Hz lower than the crossover frequency.
    - Deviations to frequency boundaries may be allowed based on clinical experience and subject performance.
  - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4)
- Arm 2
  - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4, default frequency boundaries)

6.2.7 9-MONTH

6.2.7.1 TESTING – TEST ORDER AND WORD LISTS RANDOMIZED

- Unaided pure tone thresholds in both ears, including 125 Hz.

- Soundfield thresholds, measured using warble tones, with the SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary).
    - Arm 1 participants will be tested in their EAS Map.
    - Arm 2 participants will be tested in a familiar, CI-alone map.
- Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, EAS Map (Arm 1) or familiar, CI-alone map (Arm 2)
    - CNC Words
    - Question/Statement Test
- Arm 1 only: Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, HA portion only.
    - CNC Words
    - Question/Statement Test
- Pediatric SSQ

6.2.7.2 FITTING

- Arm 1
    - Fit to DSL targets through 70 dB HL audiometric threshold (crossover frequency) using measured RECDs.
    - Set the most apical electrode frequency boundary for 100 Hz lower than the crossover frequency.
        - Deviations to frequency boundaries may be allowed based on clinical experience and subject performance.
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4)
- Arm 2
    - Programming using standard clinic procedures and software defaults (natural directionality, mild wind noise reduction, FS4, default frequency boundaries)

6.2.8 12-MONTH

6.2.8.1 TESTING – TEST ORDER AND WORD LISTS RANDOMIZED

- Unaided pure tone thresholds in both ears, including 125 Hz.
- Soundfield thresholds, measured using warble tones, with the SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary).
    - Arm 1 participants will be tested in their EAS Map.
    - Arm 2 participants will be tested in a familiar, CI-alone map.
- Soundfield testing, SONNET/SONNET 2 EAS alone (Arm 1) or SONNET/SONNET 2 (Arm 2) (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, EAS Map (Arm 1) or familiar, CI-alone map (Arm 2)
    - CNC Words

  - BKB-SIN
  - Question/Statement Test
- Arm 1 only: Soundfield testing, SONNET/SONNET 2 EAS alone (contralateral ear plugged and masked if necessary), 60 dB SPL, 0 degrees, HA portion alone.
  - CNC Words
  - BKB-SIN
  - Question/Statement Test
- Pediatric SSQ
- OWLS II
- GFTA III

6.2.8.2 FITTING

- Program based on best practices and standard clinical procedures based on the results of today's testing.

6.3 ACCOUNTABILITY

The MED-EL SONNET/SONNET 2 EAS is routinely fit off-label in our practice and can be ordered as part of the initial stimulation kit. These kits are ordered at the time of surgery, prior to enrollment. Registration of these devices is kept as part of the medical file. The specific device serial numbers will be kept in the regulatory binder as well.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects in Arm 1 may be moved to Arm 2. If a subject loses residual hearing and no longer falls within the inclusion criteria, they will remain enrolled in the study, but will be shifted to Arm 2.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are assigned but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are assigned and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

Subjects will continue to be followed for regular CI programming by the clinical CI team if they are withdrawn. Data collection for this study will stop following withdrawal.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 5 months and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 3 working days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

BKB-SIN: The BKB-SIN is a speech-in noise test that uses the BKB (Bamford-Kowal-Bench) sentences, recorded in four-talker babble. The BKB-SIN is quick and easy to administer and score, contains age-related norms for children, is suitable for CI users, and is less susceptible to ceiling effects.

CNC: A standardized word list comprised of 50 words with consonant-vowel-consonant construction ie, Consonant-Nucleus-Consonant (CNC) words (Peterson & Lehiste, 1962). The CNC test assesses perception of monosyllabic words. The test includes 10 lists of 50 words each. Each word is preceded by a carrier word "ready."

Desired Sensation Level (DSL): The DSL Method was originally developed to provide audiologists with a systematic, science-based approach to pediatric hearing instrument fitting that ensures audibility of amplified speech by accounting for factors that are uniquely associated with the provision of amplification to infants and young children who have hearing loss (Seewald, Ross and Spiro, 1985; Ross and Seewald, 1988; Seewald and Ross, 1988).

Goldman-Fristoe Test of Articulation (3rd Ed) (GFTA 3): This test is administered to assess a child's phoneme production in single words. Standard scores are based on a mean of 100 and standard deviation of 15.

Leiter-R: The Leiter International Performance Scale-Revised (Roid & Miller, 1997) is a nonverbal measure of intellectual functioning normed for individuals between the ages of 2 years 0 months and 20 years 11 months.

Oral and Written Language Scales (2nd Ed) (OWLS II): *This test assesses receptive (understanding of language) and expressive (use of language) language for children and young adults aged 3 through 21 years. Standard scores are based on a mean of 100 and standard deviation of 15.*

Speech, Spatial and Qualities of Hearing Scale (SSQ): (Gatehouse & Noble, 2004). The SSQ questionnaire assesses performance in three domains, hearing speech in quiet and noise environments (9 items), spatial or directional hearing (5 items) and sound qualities (8 items), which address sound segregation and listening effort. Each item is rated on a 10-point scale. Domain scores represent an average of item ratings. There is a version for children that will be used for this study.

The Question/Answer Task (Peng et al, 2012): Evaluates a listener's ability to identify statements vs questions using listening alone.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Anticipated Events: those events described as potential risks in the protocol.

Unanticipated Events: Events not reported as potential risks.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Unanticipated serious adverse events are defined as any serious adverse event related to the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that event, problem, or death that was not previously defined 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 participants.

Serious Adverse Event: Serious injury means an injury or illness that: 1) is life-threatening, 2) results in permanent impairment of a body function or permanent damage to a body structure, or 3) necessitates medical or surgical intervention to preclude permanent impairment to a body function or permanent damage to a body structure.

Permanent means an irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

8.2.3 ADVERSE EVENT REPORTING

All adverse events will be recorded and tracked using an Adverse Event Report Form. These forms will be reviewed by the sponsor/PI and will be followed until satisfactory resolution. Frequent adverse events will be discussed with co-investigators.

Anticipated events will be reported to the IRB in the annual report.

Unanticipated events will be reported to the IRB within 10 days of the investigator becoming aware of the event.

8.2.4 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete a Serious Adverse Event Form and submit to the study sponsor/PI and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor/PI is responsible for conducting an evaluation of an SAE and shall report the results of such evaluation to the IRB and participating investigators within 10 working days after the sponsor/PI first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as the IRB requests.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor/PI and should be provided as soon as possible.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

- A power calculation utilizing CNC scores obtained from the pilot data determined that a minimum of 9 evaluable subjects would provide at least 90% power. A sample size of 20 participants per arm was selected due to known variability in pediatric CI recipient outcomes and the possibility of those with progressive loss moving from Arm 1 to Arm 2. Sample size was calculated via G*Power 3.1.9.2 and the following assumptions were made:
    - Paired t-tests
    - One-sided 0.05 alpha levels
    - Desire for 90% power
    - Assumed distribution (mean, standard deviation) based on pilot data.

9.2 STATISTICAL PLAN

- Descriptive summaries will be provided for the following:
    - Participant demographics
    - Frequency of major and minor complications/adverse events.
- A single-subject design will be utilized, where each participant serves as his or her own control, for analysis of objective and subjective results. A single-subject design was chosen in order to accommodate the heterogeneity that is well known to characterize auditory prosthesis research.
- Considering the possibility of subjects moving from Arm 1 to Arm 2, mixed-design ANOVA will be calculated with a p-value of ≤ 0.05 for statistical significance.
- Effect sizes and confidence intervals of 95% will be calculated and reported for primary endpoints.

- Normality will be evaluated based on visual inspection of the data and using Kolmogorov-Smirnov test. These steps will be used prior to all statistical analyses at the 12-month endpoint..
- Bonferroni corrections for multiple tests (n=2) will be applied to analyses of the primary endpoints.
- Statistical analysis will be conducted with SPSS software.
- The following measures will be analyzed:
    - Comparison of CNC scores between conditions and groups.
    - The distributions of CNC word scores will be evaluated for assumptions of normality. Depending on the outcome, comparisons will be made with paired t-test or Mann-Whitney test. Comparison of BKB-SIN scores between conditions and groups.
        - The SNR-50 score is computed based on an algorithm that is implemented in the test materials. It is an estimate of the signal-to-noise ratio associated with 50% correct based on word-level scoring.
        - Distributions will be evaluated for assumptions of normality. Depending on the outcome, comparisons will be made with paired t-test or Mann-Whitney test.
    - Comparison of Pediatric SSQ subjective report scores in the pre- and post-initial activation intervals.
    - The distributions Pediatric SSQ scores will be evaluated for assumptions of normality. Depending on the outcome, comparisons will be made with paired t-test or Wilcoxon Signed Rank test. Comparison of pre- and post-operative speech and language scores (OWLS II and GFTA) between groups.
        - The distributions of articulation and language scores will be evaluated for assumptions of normality. Depending on the outcome, comparisons will be made with paired t-test or Mann-Whitney test.
    - Comparison of prosodic discrimination abilities between conditions and groups.
- If needed, statistical consultation will be sought from the North Carolina Translational and Clinical Sciences Institute (TraCS) or UNC Odum Institute.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant's parent(s)/guardian(s) and written documentation of informed consent is required prior to starting intervention. Assent forms will be given to subjects over the age of 7. Signed copies will be given to participants.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent and assent forms will be

Institutional Review Board (IRB)-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and family and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent and assent forms and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document and assent form will be given to the participants' guardian for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Communication will occur in a closed-door room at the Children's Cochlear Implant Center and/or the Clinical Research Lab at the Children's Cochlear Implant Center.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators. All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), regulatory agencies, or the manufacturer may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records. When data is pulled from the database for analysis, no identifying information will be kept with the data.

Upon enrollment, all subjects will be assigned an anonymous subject ID. The subject ID will be stored in a password protected FileMaker database housed on a UNC server. This will be linked to the subject's name, but this information is only viewable by study personnel. The study coordinator will enter all of the subject's demographic information and test results into this database. All personal identifiers will be kept separate from the study data.

Subject specific binders will be maintained in a locked cabinet in the Children's Cochlear Implant Center. Individual data collection sheets will be coded with the subject number, and placed in the subject specific binder at each interval.

10.1.3 QUALITY CONTROL

We will perform internal quality management of documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated with the investigator for clarification/resolution.

10.1.4 DATA HANDLING AND RECORD KEEPING

10.1.4.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Subjects will be assigned a specific alpha-numeric participation code upon enrollment. The linkage file for that code will be stored in a password protected, customized FileMaker database secured on UNC servers. Only co-investigators will have access to this file.

Data collection is the responsibility of the clinical trial staff under the supervision of the PI. Each investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

The data will be recorded on Case Report Forms (CRFs) in patient-specific binders on a case-by case basis after each subject encounter. CRFs and source documents will not contain identifiable information. Hardcopies of the CRFs and source documents will be maintained in the study binders. Data recorded on Case Report Forms should be consistent with the data recorded on the source documents. The study coordinator will verify consistency. Subject binders will be stored in a locked cabinet at The Children's Cochlear Implant Center at UNC.

Clinical data (including adverse events (AEs)) will be entered into the FileMaker database. Only co-investigators will have access to this data. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. A customized database will be used for this study. Only subject IDs will be used when entering data. Clinical data will be entered directly from the CRFs.

The co-investigators will be responsible for data entry and for cross checking data for accuracy. At the time of data analysis the data will be exported by desired field to an Microsoft Excel spreadsheet for further analysis. Any use of the data outside of the database will employ the subject ID and will not include personal identifiers

10.1.4.2 STUDY RECORDS RETENTION

After the closure of the study, subject data will be retained for seven years. At that time, paper data will be shredded and destroyed in a HIPAA compliant manner. Electronic data will be destroyed following UNC policy.

10.1.5 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1

- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study documents. Protocol deviations will be reported to the IRB as part of the annual report.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
V1.1	11/21/17	Incorporated Scientific Review Committee suggestions	
V1.2	5/4/2018	Will be doing the Pediatric SSQ rather than the Peds-QL	Peds QL is not proving to be a good measure of fatigue in another ongoing study. The pediatric SSQ is providing much more valid data.
V1.3	9/22/2018	Testing in HA condition rather than CI alone in Arm 1 participants	This will allow us to compare to pre-operative scores and account for developmental aspects. In addition, the CI alone condition would be novel and unfamiliar in this group, likely making for an invalid measurement. We can instead use the Arm 2 participants for comparison as they will have adapted to a full CI program.
V1.4	11/1/2018	Changing inclusion criteria to include 5-year-olds and children with a composite language score down to 60.	Effort to ease recruitment. Five-year-olds with residual hearing are capable of completing the test protocol. Many potential candidates have language skills that are poorer than we expected, and we want to be able to include these children and measure changes in language abilities as well. A standard score of 60 would avoid floor effects and still include children who are able to complete the test protocol.
V1.5	11/18/2019	Changing exclusion criteria to specify that a neurotologist will read scans of potential candidates under a waiver of HIPAA to confirm a lack of cochlear nerve deficiency.	This change is in response to the withdrawal of a subject who was noted to have CND after enrolment.

V1.6	12/3/2019	Added SONNET 2 EAS as a device. Removed Maestro 7 as a device and changed to simply include the Maestro System.	SONNET 2 EAS has been FDA approved and will be arriving in patient kits. It is an updated version of the SONNET EAS device. Maestro 7 is no longer considered experimental and we will be using the FDA approved versions of the software from this point on as they now provide what we need to fit the EAS devices.
V1.7	5/18/2020	Removing Leiter-R from protocol and changing exclusion criteria to read "known or suspected cognitive impairment." Changing screening procedures.	The Leiter-R has proven to be an unnecessary and cumbersome measure. For safety measures in light of COVID-19 it is being removed as a screening tool. To ease scheduling difficulties in light of COVID-19, investigators may reach out to potential candidates prior to initial stimulation to discuss the study and schedule initial stimulation visits appropriately.

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12 ABBREVIATIONS

CI	Cochlear Implant
EAS	Electric-Acoustic Stimulation
CNC	Consonant-Nucleus-Consonant
BKB-SIN	Bamford-Kowal-Bench - Speech in Noise Test
Pediatric SSQ	Pediatric Speech, Spatial, and Qualities Questionaire
GFTA 3	Goldman Fristoe Test of Articulation – 3rd edition
OWLS II	Oral and Written Language Scales – 2nd edition
LFPTA	Low Frequency Pure Tone Average (Average of thresholds at 125, 250, and 500 Hz)
CRF	Case Report Form
RIC	Receiver in the Canal
SNR-50	Signal to Noise Ratio required for 50% performance
SoA	Schedule of Activities
CONSORT	Consolidated Standards of Reporting Trials
SAE	Serious Adverse Event
AGC	Automatic Gain Control
dB	Decibel
SPL	Sound Pressure Level
HL	Hearing Level
V	Volts
Hz	Hertz
Ω	Ohms
KHz	KiloHertz
G	Grams
RECD	Real Ear to Coupler Difference
DSL	Desired Sensation Level
RF	Radio Frequency
FS4	Fine Structure 4 channel
P1, P2, etc.	Program 1, Program 2, etc.
AE	Adverse Event
PI	Primary Investigator
IRB	Institutional Review Board
HA	Hearing Aid